Carbohydrate metabolism

The metabolism of the sugars found in our food is discussed in all textbooks and I will not take up all of the details here. The points I do wish to discuss are concerned with maintenance of blood sugar levels under differing physiological conditions. How do we start up storage of glucose after a meal? How do we preserve blood glucose levels between meals? What are the differences in metabolism of common sugars in various organs?

Transport of Glucose in and out of the Liver

The whole thing begins with transport of sugars over tissue membranes. These "small" sugars (glucose, fructose and galactose) are so large that they cannot cross cell membranes without "carriers". Sugar carriers are proteins embedded in the cell's outer membrane that provide transport systems for monosaccharides. The glucose transport protein family (called GLUT) is discussed elsewhere in MedBio. Click here for more information. The point to note now is that these carriers are bidirectional; they can transport glucose both into and out of cells.

Hepatic Glucose Transport

1. Glucose

2. Glucose

3. Glucose

The direction of movement is determined by the concentrations of glucose in and outside of the liver cell. This is illustrated in the figure above.
Drawing "1" shows the situation when the portal blood and the liver cell have equal concentrations of glucose; sugar moves in both directions simultaneously. This may seem to be wasteful, but gears the system to react to small changes in glucose concentration.

The second drawing shows what happens when blood glucose tends to fall. Glucose production in the liver accelerates and the net flow of glucose is outward, stabilizing the blood sugar level. This is extremely important. The total amount of sugar present in the blood can support resting activity for about 40 minutes. Just walking increases glucose use to a point where the entire blood content is used up in about 15 minutes. Since mental activity is completely dependent upon stable blood glucose levels, there must be a way of evening out blood glucose levels. This is one of the major duties of the liver. On a short-term basis, this is the only organ capable of replacing blood sugar used by other organs. Click here for the details.

Following a meal, the portal blood sugar level increases. This is shown in the third drawing where we see that the liver rapidly takes up glucose from the blood. Once again, the liver stabilizes blood sugar. In principle, this two-way flow of glucose can forego in most tissues. However, only the liver and kidneys are sugar producers and export of glucose occurs only in these tissues. Most of our organs are sugar-burners, taking up glucose from the blood and using it for energy production.

What determines this limit on release of glucose from most of the body? Why cannot skeletal muscles release glucose from their large glycogen stores? The secret is that uptake of sugars to our organs involves immediate phosphorylation at either carbon 1 or 6. The phosphorylated sugar derivatives cannot "leak" out of the cell. There is no mechanism for their cross-membrane transport. Once sugars are phosphorylated they stay put!

What is the key to production of glucose in the liver and kidneys? These organs produce a specific enzyme, glucose-6-phosphatase, that cleaves the glucose-phosphate bond. Regulation of the balance between phosphorylating and dephosphorylating enzymes is crucial and determines the net direction of uptake and release of glucose in these organs.
Regulation of sugar phosphorylation

As stated above, monosaccharides enter metabolism through phosphorylation. That is, they react with ATP and a kinase to yield phosphorylated derivatives. Those small structural differences we noted between the three monosaccharides found in our food determine which enzyme initiates sugar metabolism. Glucose can be phosphorylated by either hexokinase or glucokinase. The former is involved in the cell’s energy metabolism. Glucokinase is implicated in either energy storage or in glucose-signaling systems. Fructose metabolism is initiated through fructokinase while galactokinase is the first enzyme involved in galactose metabolism.
All organs exhibit hexokinase activity. As the name implies, this enzyme is relatively nonspecific and can react with most 6-carbon sugars. However, its affinity for these sugars varies with their structure. Hexokinase reacts strongly with glucose at levels found in plasma and tissues. While it in principle can catalyze phosphorylation of fructose and galactose, its affinity for these is quite low. This excludes active handling of fructose and galactose by hexokinase at the concentrations of these found in our bodies. Hexokinase is product-inhibited. That is, if the glucose-6-phosphate formed by the enzyme is not rapidly removed, hexokinase activity promptly falls. Hexokinase is well-adapted as the first enzyme in tissues utilizing glucose as an energy source, but not as the initiator of energy storage in the liver. We find, therefore, specialized kinases in the liver to handle all three of the sugars found in food. The following table summarizes the distribution and substrate specificity of the kinases involved in the initiation of sugar metabolism. Note that glucokinase is found in tissues that require a "glucose sensing system". I’ll come back to this under a discussion of insulin secretion.

Note also that it is the liver that has fructokinase and galactokinase activity. The liver is the only organ that actively metabolizes these sugars. I will take up replacing table sugar with fructose later but you can see now that fructose is a substrate for hepatic metabolism alone. Aside from sperm, no other organ has an active fructokinase. No other organ is perfused with concentrations of fructose large enough to allow reaction with hexokinase. The liver very effectively removes absorbed fructose from the portal blood. In fact, this is necessary for uptake of fructose in the gut. Remember that transport there is passive, relying on a steep concentration gradient to drive fructose uptake. Fructose is not a direct energy source for muscles and the brain as many of its producers claim. These tissues rely on the hexokinase catalyzed phosphorylation of glucose for

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Km (glucose)</th>
<th>Km (fructose)</th>
<th>Km (galactose)</th>
<th>Physiological substrate</th>
<th>Product</th>
<th>Found in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexokinase</td>
<td>0.05 mM</td>
<td>1.6 mM</td>
<td>1.2 mM</td>
<td>Glucose</td>
<td>G-6-P</td>
<td>All organs</td>
</tr>
<tr>
<td>Glucokinase</td>
<td>5-12 mM</td>
<td>-</td>
<td>-</td>
<td>Glucose</td>
<td>G-6-P</td>
<td>Liver, 6-cells of hypothalamus</td>
</tr>
<tr>
<td>Fructokinase</td>
<td>-</td>
<td>Low!</td>
<td>-</td>
<td>Fructose</td>
<td>F-1-P</td>
<td>Liver</td>
</tr>
<tr>
<td>Galactokinase</td>
<td>-</td>
<td>-</td>
<td>Low!</td>
<td>Galactose</td>
<td>G-1-P</td>
<td>Liver</td>
</tr>
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energy metabolism. Sorry, but you do not become stronger and smarter by eating fructose.

**Glucose metabolism and glucokinase**

Let us take up glucokinase first. This enzyme is specific for glucose and is not inhibited by its product, glucose-6-phosphate. While glucokinase has a high $K_m$ (low affinity) for its substrate, it reacts strongly with glucose at the concentrations found in portal blood after a carbohydrate meal. The $K_m$ of the liver enzyme, around 10-12 mmolar, lies above fasting blood glucose levels. This means that glucokinase activity is "turned on" by the glucose in portal blood following a meal (10-30 mmolar), and is "turned off" after glucose from the meal is absorbed. Remember, a major function of the liver is to release glucose when blood sugar levels begin to fall. Liver has an enzyme (glucose-6-phosphatase) that cleaves phosphate from glucose-6-phosphate, yielding free glucose. The balance between glucokinase and glucose-6-phosphatase slides back and forth, increasing uptake to the liver when the level of blood glucose is high, and releasing glucose when blood glucose falls. It was commonly believed that this $K_m$-steered regulation of glucokinase was the key to understanding glucose uptake and release in the liver. However, we now know that a much more refined mechanism controls glucokinase activity.

**Translocation of glucokinase between cytosol and nucleus**

Hepatic glucokinase has a high $K_m$ and this will serve as a "switch" to activate and inactivate the enzyme. But, think about the situation which evolves when blood glucose tends to fall. Glucose is synthesized from stored glycogen and through gluconeogenesis. The cytoplasmic concentration of glucose must rise if the liver shall export sugar and this would "turn on" glucokinase, drive forward phosphorylation and spoil the system. And that at a time when glucokinase must be inactivated to allow glucose dephosphorylation and export. So, how do we stop glucokinase activity?
One of the best ways to "turn off" an enzyme is to put it away. Just move the protein to a compartment where it is not needed and inactivate it by binding to a parking place! Several publications during the past few years have shown that glucokinase is translocated to the liver cell's nucleus when plasma glucose concentrations approach fasting levels (around 5mmoles/l). It is bound there to a glucokinase regulatory protein called GKRP. Release and translocation back to the cytosol is stimulated by increases in plasma glucose, trace amounts of fructose, and insulin. This translocation system may well be dominant in directing glucose flow in and out of the hepatocyte. The following figure is taken from "Regulation of Hepatic Glucose Metabolism by Translocation of Glucokinase between the Nucleus and the Cytoplasm in Hepatocytes", Y. Toyoda et. al., Horm Metab Res 33, 329-336 (2001). The bright areas in the pictures are immunofluorescent areas in hepatocytes in culture. The fluorescence comes from glucokinase. Clearly, the enzyme moves from the nuclei to the cytosol when glucose levels in the surrounding medium is increased from 5 to 25 mmol/liter. Small amounts of fructose greatly promote this transfer.

While the total GK activity (cytoplasmic plus nuclear activity) was not altered after incubation with glucose, the enzyme migrated from the nuclei to the cytosol in these cells. Inclusion of fructose at very low levels led to increased cytoplasmic glucokinase at 5 mM, and appeared to give a total transfer to the
In summary, glucose, insulin and fructose control the activity of glucokinase through translocation in liver cells. Storage of active enzymes and carriers as a method of metabolic control has been well-documented previously with respect to the insulin-sensitive glucose carrier GLUT4.
Fructose Metabolism and its Influence on Glucose Metabolism

One of the strange things here is the role of fructose. Why is fructose such a strong signal for release of glucokinase. Remember, glucokinase is "not interested" in reacting with fructose. It is specific for glucose. The enzyme required to initiate fructose metabolism, fructokinase, is only found in quantity in the liver (and sperm cells). Furthermore, it is not under metabolic control. If fructose comes to the liver, it will be taken up and very quickly metabolized!

Carbohydrate metabolism starting from glucose or galactose proceeds under strict control; fructose is in a special class! We are "constructed" to conserve energy. The rapid entry of fructose into glycolysis leads to fatty acid synthesis in the liver. Because fructose metabolism "fills" glycolysis with substrate at a very high rate, frequent use of sucrose (remember sucrose is a dimer of fructose and glucose) or fructose promotes fat production. Plasma triglyceride levels are increased by the ingestion of large amounts of sugar. There is a correlation between sugar consumption, high plasma lipid levels and atherosclerosis.

Starch, which yields glucose during digestion, has been a main energy source for mankind since the agricultural revolution 8000-10000 years ago. Fructose is found in small quantities in many fruits and honey. The amount of fructose in our diets was far lower than starch-derived glucose found in the food we have eaten for thousands of years. Combine an apple (5-7% fructose) and some wheat, potatoes or corn, and you get translocation of glucokinase and an active glucose metabolizing system (with a little fructose taken along for the ride). Fructose seems to have acted as a signal substance, used to activate glucose metabolism.

Fructose in our diet

Commercial production of fructose began in Finland in 1969. Since then it has become "modern" to exchange fructose for sugar to cut down on the caloric content of sweetened food. Fructose is sweeter than sucrose. But, it is the 5-ring form of fructose that is sweet, the 6-ring form tastes about the same as usual table sugar. Unfortunately, warming fructose leads to formation of the 6-ring form. Sweetening coffee and tea and baking cakes with fructose requires just about as much of this sugar as sucrose to get the same taste. Baking is also difficult as one needs to use about the same amount of fructose as table sugar and it burns at lower temperatures.

By the way, shifting out sucrose with less fructose may reduce total calorie intake, but it increases fructose consumption. Statistics from the USA suggest that people
do not cut back sugar use when they use fructose. They seem to choose sweeter food! Remember, half of table sugar is fructose, all of fructose is fructose! That excess fructose will be largely converted to fat!

The new sweetener, high fructose corn syrup (HFCS)

While consumption of sucrose has actually fallen in the USA, the use of high-fructose corn syrup (HFCS) has increased markedly during the past 30 years. Conservative estimates suggest that 16% of the energy intake of average Americans is fructose. HFCS contains either 42% or 55% fructose. This is produced from corn through hydrolysis of starch. The resulting glucose syrup is then isomerized to the sweeter high fructose syrup enzymatically. High fructose corn syrup is widely used today in commercial production of soft drinks, breakfast cereals, baked goods and condiments. As we can see from the following figure

Sugars in the American Diet, 1970-1997

from Elliott et.al., total sugar consumption has increased in the USA during the past 30 years despite a real fall in sucrose consumption. The decreased use of sucrose is more than balanced by substituting fructose for sugar in commercial food production. The global distribution of soft drinks, breakfast cereals and fast food is leading to similar increases in sugar consumption in many areas.

Fructose does not cause insulin release from beta cells, as these lack fructokinase. One of the results of this is that fructose consumption does not dampen appetite. This may lead to increased caloric intake with obesity and the metabolic syndrome as a result. You can read more about fructose, weight gain and insulin resistance in an excellent article by Elliott et al, Am J Clin Nutr 76, 911-922 (2002). Just click here if you have access to a library.
In the next 3 figures I will try to clarify this fructose business. First, remember that sugars do not just diffuse through the hepatocytes plasma membrane. There must be a carrier there or they “cannot come in”. That carrier is GLUT2. This glucose transport protein reacts with both fructose and glucose.

Let us take up interaction with glucose first.

Once again, recall that glucose transporters carry sugar down a concentration gradient. If glucose concentration is high in portal blood, the liver will take up glucose. This will be stored as glycogen which can later be used to replace blood sugar. Part of the glucose load is oxidized completely to CO$_2$ and drives ATP production. Excess carbohydrates are converted to fatty acids and exported as triglycerides. The trace of fructose found in food gives F-1-P and this serves as part of the glucokinase activating system. Thus, low levels of fructose, judged by today’s urban standards, activate uptake and metabolism of glucose.
Falling levels of glucose in the blood flowing through the liver favor glucose export, shown in the next figure. Hormone activation of hepatic gluconeogenesis and glycogenolysis lead to increased hepatic glucose concentrations and export of glucose. The direction is determined through allosteric and hormonal control of the enzymes involved. The final actors in this picture are glucokinase and glucose-6-phosphatase. Recall that release of glucose from the liver demands stopping glucokinase activity. As I hope I have explained above, glucokinase activity is controlled to a large degree by "parking" the enzyme in the hepatocyte's nucleus (or nuclei; they are often binuclear). The absence of fructose in the portal blood assures minimal F-1-P concentrations: Glucokinase can be "parked" in the cell's nucleus.
Sugar and Fructose metabolism

So, what happens if we consume large quantities of table sugar (sucrose) or high fructose corn syrup? The body responds to the glucose content of the meal in the usual manner; insulin secretion increases and glycogen and lipid metabolism proceed as would be expected. However, fructose uptake and phosphorylation occurs at the same time, providing additional substrate for these anabolic processes. Remember that fructose does not stimulate insulin secretion. The hormonal steering of metabolism applies only to that induced by glucose. The excess substrate from fructose is poured into fat synthesis which is stimulated by the insulin released in response to simultaneously consumed glucose.

Hepatic Glucose and Fructose Metabolism After Sugar Consumption

The liver has a huge capacity for the uptake and phosphorylation of fructose. The phosphorylation capability is about twice that of the glucose phosphorylation system. We find large increases in uptake and metabolism of fructose with increased sugar levels in portal blood. In individuals with fructose intolerance we find an increase in fructose-1-phosphate due to the fact that fructokinase activity can exceed that of aldolase B. This special aldolase is required to cleave F-1-P to dihydroxyacetone phosphate and glyceraldehyde. The fructose taken up cannot be stored as such. It is converted to intermediates in glycolysis WHICH COME AFTER THAT ALL-IMPORTANT CONTROL POINT, PHOSPHOFRUCTOKINASE 1. So what? Well, some of that fructose winds up as glycogen and glucose. That is ok; we need glucose in the blood. The rest of the fructose rushes through pyruvate, is transferred to mitochondria, and finally converted to fatty acids and exported from the liver as triglycerides.

That fat formation is a major problem. People that consume large amounts of sugar seem to demonstrate increased plasma triglyceride levels. This is quite parallel to eating large quantities of saturated fats. While the mechanisms here
are not completely clarified, there is good reason to believe that increased plasma triglyceride are a moment in development of atherosclerosis and CVD.

So, why do we have such an active fructose metabolism in the liver? Speculation again, but an interesting hypothesis is that traces of fructose in the blood perfusing the liver indicate consumption of carbohydrates and a need for glucokinase release and activation. As is the case in many other physiological systems, it may well be that a combination of hormonal and allosteric factors steer the body's reactions. Fructose may have initially been a signal stuff. The "new" today is that it has become a major energy source in the diet.

To summarize and Speculate a little:

Control of the ratio of glucokinase and glucose-6-phosphatase activity is essential for regulation of the liver's uptake and release of glucose. Control of the blood glucose level is vital for mental processes. In fact, a 50% cut in blood glucose levels leads to dizziness, nausea and eventually loss of consciousness.

Our diet through thousands of years included starches as the major carbohydrate source and fructose as a sweet extra in fruits and honey. Remember, progression to the "hunter stadium" came long after development of the first humanoids. You can click here to find more information about this. A very active conversion of that limited fructose to fructose-1-phosphate (not 6-phosphate) appears to have been elemental in regulation of hepatic glucokinase and glucose metabolism. The epidemic growth of overweight, diabetes type 2, hypertension and CVD in urban societies around the globe today may well have our exceedingly high sugar consumption as a major underlying factor. We were simply "not made" to eat 25% of our food in the form of sugar. Changing to fructose will not help!

Table sugar and fructose used as a "spice" also provide excess calories and resulting obesity. Perhaps the most important thing to remember here is that excessive chronic sugar intake can lead to increased plasma fatty acid concentrations with the danger of developing atherosclerosis. In susceptible individuals this may lead to metabolic syndrome and associated diabetes type 2, hypertension, and damage the kidneys. For a deeper discussion of the metabolic syndrome click here.
Hereditary fructose intolerance disease

As stated above, hepatic fructose metabolism is quite rapid. That is, the initial step, phosphorylation by fructokinase is rapid. Further metabolism of fructose is dependent upon aldolase B. Normally, fructose consumption leads to a rapid flux into glycolysis at the triose phosphate level, enhancing gluconeogenesis, glycolysis and triglyceride synthesis. However, individuals who have reduced levels of aldolase B exhibit so-called fructose intolerance. They build up excessively high hepatic fructose-1-phosphate levels, trapping inorganic phosphate and reducing ATP synthesis accordingly. In these people, fructose is not a good substrate for glycolysis or gluconeogenesis.

While the statistics on this are not clear, it appears that somewhere between 1 in 10,000 to 1 in 50,000 persons exhibit fructose intolerance. Declining ATP levels interfere with many of the liver's functions, among these are ureogenesis and gluconeogenesis. You can get more information about fructose intolerance syndrome by clicking here.
To summarize, reducing calorie intake by using fructose instead of sucrose does not give big winnings. And there is that fat synthesis business. And, not least important, metabolism of fructose happens in the liver. One does not get extra and long-lasting energy from fructose as suggested on some fructose packages! Muscles and the brain get energy from fructose only after the liver has converted fructose to glucose or fat.

Galactose metabolism

Carbohydrates in food give us only three monosaccharides that are taken up from the intestine and metabolized further. Go back to the chapter on the structure of sugars to review this (it’s just a click away). Remember, sucrose (table sugar) gives us equal amounts of glucose and fructose, lactose (milk sugar) gives equal amounts of galactose and glucose.

Galactose is almost identical to glucose; remember it is only the position of the hydroxy group on carbon four that differs here. That "little" difference is enough to markedly reduce binding of galactose to hexokinase. A specific enzyme, galactokinase, is essential to initiate galactose metabolism. Galactokinase reacts with galactose and gives us galactose-1-phosphate. There is no direct oxidative pathway for galactose-1-P. It has to be converted to an intermediate in glucose metabolism to come further. We have an activated form of glucose, uridine diphosphoglucose (UDPG) that reacts with gal-1-P. UDPG has a glucose-1-P "tail". Using UDPG-gal-1-P transferase, we simply exchange that "tail" with gal-1-P and convert the Gal-1-P to glucose-1-P. Another enzyme, UDPGal-UDPG isomerase "wins" back that UDPG for us and the process can start up again.
Unlike fructose metabolism, glucose and galactose metabolism are subject to precise allosteric and hormonal control. Metabolism of these sugars goes through phosphofructokinase and FDPase, two enzymes under exacting hormonal and allosteric control.

The metabolism of galactose is usually non-problematic for those of us who have lactase (the enzyme which splits lactose). All of the others (about 90% of the world's adult population) are lactose intolerant and cannot consume milk and milk products unless these are fermented first. Recall that lactase is a very special enzyme, the only one we have that can split the β-sugar bond. No lactase, no hydrolysis of milk sugar. That means that lactose will be sent to the large intestine giving "explosive diarrhea".

Galactose intolerance does occur in children lacking either galactokinase or the converting enzyme galactose-1-phosphate-UDPG transferase. In the latter case, phosphorylated galactose levels build up in the liver, trapping inorganic phosphate and preventing ATP production. This will "knockout" liver functions and lead to low blood sugar levels and brain damage all too quickly. All newborn babies are controlled for galactosemia during the first few days of life. They are switched from a milk diet to one based on sucrose if they have excessive plasma galactose.
There is something strange about lactate...

We usually think of pyruvic and lactic acids as normal end products of glycolysis. Release of lactate follows increased energy utilization, especially in skeletal muscles. Anaerobic glycolysis is something that extra work brings forth. What we often neglect is that some tissues serve as "lactate producers" with the intention of nourishing others.

Perhaps the easiest to understand here are erythrocytes. After all, they do not have mitochondria and cannot oxidize glucose to CO$_2$. Furthermore, glycolysis in these cells is largely inefficient. Erythrocytes produce (and require) 2-3 bisphosphoglycerate in amounts about equal to their hemoglobin content. While this gives control over oxygen-binding to hemoglobin it precludes a net production of ATP. Erythrocytes can take up and metabolize quantities of glucose without the inhibitory effects of high ATP levels. What happens to all that lactate? It just so happens that our kidneys thrive on lactate and devour as much as the red cells produce. Check the following diagram taken from the chapter about insulin. Almost 10% of the carbohydrate content of a normal meal wings up as lactate which is used as an energy substrate in the kidneys. About 2-3 g per hour are used here and most goes to aerobic metabolism and ATP production. This is a rather simple case and is perhaps not so exciting. Let's look at brain metabolism for some action!
Lactate metabolism in the brain

We have all learned that the brain (and spinal cord and retina) require a steady supply of glucose. These tissues have little or no glycogen; lack of glucose is just about as damaging as an oxygen cut in the CNS. Even under starvation, the brain must cover about 50% of its energy needs from blood sugar. β-OH butyrate and acetoacetate can supply only half of the substrate required. Why?

The blood-brain-barrier protects the brain from most substances in plasma. Even fatty acids are excluded here. And, in a way, glucose is among the excluded goodies. That is, most of the glucose that crosses the blood-brain-barrier never comes over the barrier (or glia cell). The next figure, taken from a publication by Tsacopoulou and Magistretti (click here if you are connected to a library) explains this phenomenon.

The blood-brain-barrier is comprised of glia cells, primarily astrocytes. A small fraction of the glucose released from capillaries wanders directly to nerves and synapses. However, most is “trapped” in astrocytes and oxidized to lactate by these cells. Lactate goes further into the brain and nourishes the brain’s neurons. This seems to be especially important for glutamatergic neurons which comprise much of the brain. The astrocytes also efficiently pick up released glutamate, convert this to glutamine, and send the product back to glutamatergic neurons where it continues to cycle as a neurotransmitter. The axons do not contain glycogen and are, therefore, completely dependent upon the lactate sent
from astrocytes to maintain ATP levels. Astrocytes and other glia cells appear to have some glycogen which can serve as a very short-term source of lactate.

So the answer to the preceding question is that much of the brain is dependent upon lactate from glia cells to provide substrate for aerobic energy production; ketone bodies cannot cover their substrate requirements. One can reduce glucose consumption and use ketone bodies during starvation. However, some neurons must have lactate and the brain must continue to use blood sugar.

**Testicles too...**

We find the same sort of work division in the testicles. Here, the sertoli cells enclose the seminiferous tubules, effectively shielding them from the circulation and direct uptake of glucose. This resembles the brain and the blood-brain-barrier. Substrates for energy metabolism in the tubules are delivered by the sertoli cells. These take up glucose, convert it to lactate, and send this further to the tubules. The lactate serves as the substrate of choice for spermatogenesis.