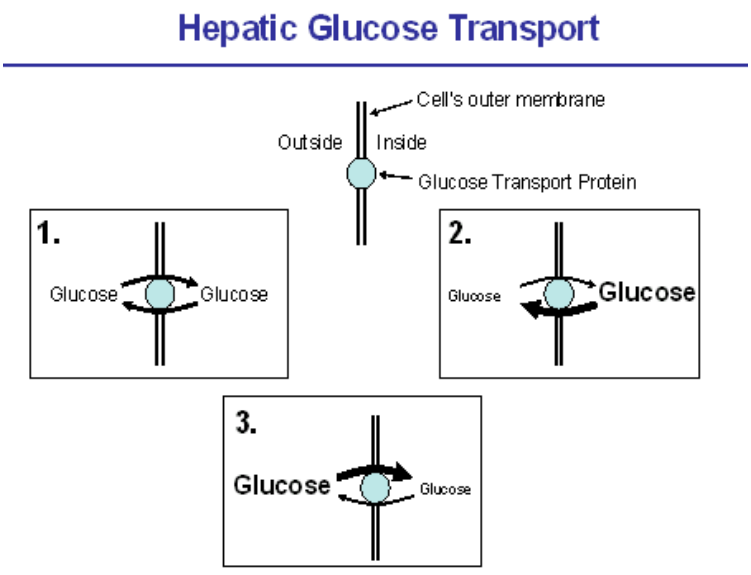
Carbohydrate metabolism

Blood sugar (glucose) is the main energy source for the brain, red blood cells and many of our muscles. Yet, blood glucose levels are more or less constant in spite of the very rapid and large turnover. This constancy is essential for normal body function. Stabile sugar levels are the result of precisely controlled chemical and hormonal feed-forward and feed-back information loops. Let us look at the basic metabolism that underlies this system and try to answer some "simple" questions. How does metabolism of sugars start? Are there differences in the metabolism of the various sugars found in the diet? How do we start up storage of glucose after a meal? How do we stabilize blood glucose levels between meals? Are the differences in metabolism of common sugars in various organs?

Transport of monosaccharides over tissue membranes.

The initial step in metabolism of sugars is their transport over the cell's outer membrane. "Small" sugars (glucose, fructose and galactose) 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. These carriers are bidirectional; they can transport glucose both into and out of cells and are driven by the concentration gradient. This, in principal, is true for all tissues. However, export of glucose from tissues to the circulation is limited to organs that produce sugar (liver and kidney) or to organs that receive sugar from the outer milieu (the small intestine). The direction of movement is determined by the differing concentrations of glucose on either side of the plasma membrane. This is illustrated in the following figure. 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 not more than 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 smoothing out blood glucose levels. This is one of the major duties of the liver which normally can produce around 200 mg of glucose per



hour. On a short-term basis, this is the only organ capable of replacing blood sugar used by other organs. Click here for the details. Gluconeogenesis in the kidneys becomes important only during prolonged fasting.

The portal blood sugar level increases markedly following a meal. 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. As mentioned above, 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. Epithelial cells in the small intestine also transport sugars into the circulation, taking sugars from the intestinal lumen and moving these to the blood. Uptake of glucose and galactose is coupled to sodium transport and Na^+-K^+ ATPase. In contrast to this, adsorption of fructose is passive or "facilitated", being driven solely by the fructose concentration gradient over cell membranes.

What determines this limit of glucose release from most of the body's tissues? 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, releasing glucose and inorganic phosphate. Regulation of the balance between phosphorylating and dephosphorylating enzymes is crucial and determines the net direction of transport of glucose in these organs.

The second step in sugar metabolism; phosphorylation.

Entry of sugar molecules into cells initiates sugar phosphorylation. That is, kinases specific for each sugar quickly catalyze interaction between the monosaccharide and ATP and yield phosphorylated derivatives. The small structural differences we noted between the three monosaccharides found in our food determine which kinase initiate their metabolism. The products resulting from the kinase catalyzed reactions differ. Let's look at phosphorylation of the three sugars which we can use as energy sources.

Tissue distribution of monosaccharide kinases.

Most 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 greatly dependent upon their structures. Hexokinase reacts strongly with glucose at levels long under those found in plasma and tissues. While it in principle can catalyze phosphorylation of fructose and galactose, its affinity for these is relatively low. Furthermore, glucose is a potent competitive inhibitor of the binding of galactose and fructose to hexokinase. This excludes active handling of fructose and galactose by hexokinase at the concentrations 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, therefore, well-adapted as the initiator of glucose metabolism in tissues utilizing glucose as an energy source, but not as the initiator of energy storage in the liver. Here we need an enzyme that is active in spite of high glucose and G-6-P levels. Glucokinase fills this role in hepatic glucose metabolism. Other specialized hepatic kinases handle fructose and galactose. The following table summarizes the distribution and substrate specificity of the kinases involved in the initiation of sugar metabolism. Note that glucokinase is also found in tissues that require a "glucose sensing system". Regulation of both insulin secretion and of appetite are functions of glucokinase.

Phosphorylation of Hexoses

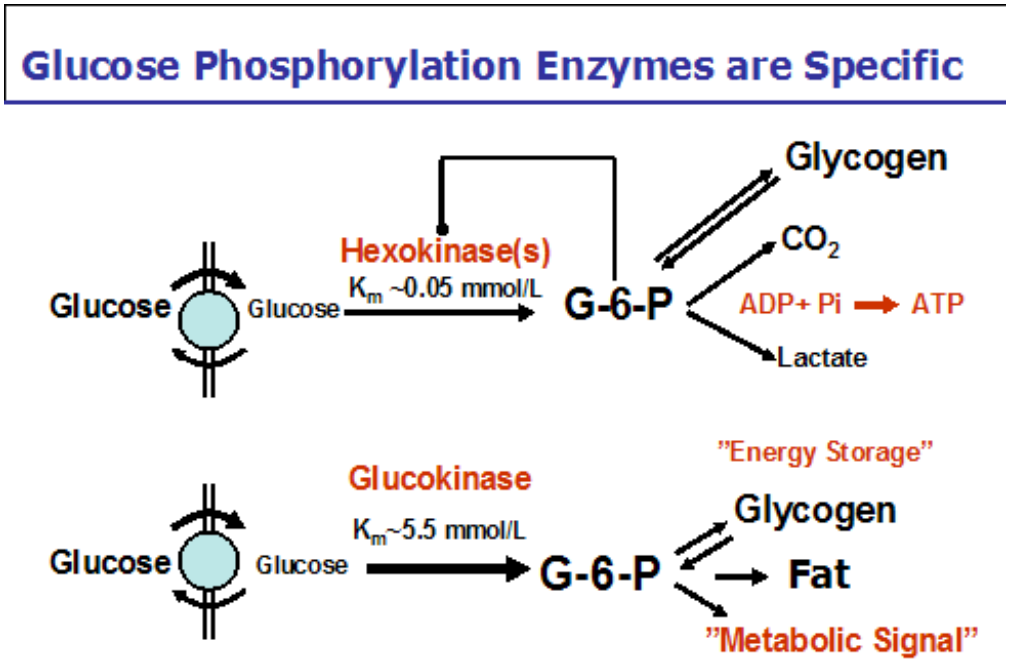
Enzyme	Km (glucose)	Km (fructose)	Km (galactose)	*Physiologic specificity*	Product	Found in
Hexokinase	~0.05mM	1.6 mM	1-2 mM	*Glucose*	G-6-P	All tissues (not ß-cell)
Glucokinase	~5.5 mM	-	-	*Glucose*	G-6-P	Liver, ß-cell, hypothalamus
Fructokinase	-	Low!	-	*Fructose*	F-1-P	Liver
Galactokinase	-	-	Low!	*Galactose*	Gal-1-P	Liver ,many other tissues

Note also that it is the liver that has both fructokinase and galactokinase activity and actively metabolizes these sugars. 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. The liver's very active fructokinase removes fructose from the circulation and permits intestinal uptake of this sugar.

Spermatozoa, which come in contact with high concentrations of fructose in the seminal fluid are the only other cells which metabolize this monosaccharide. It appears that phosphorylation of fructose in these cells is catalyzed by hexokinase rather than fructokinase as F-6-P rather than F-1-P is found in spermatozoa exposed to fructose.

Glucose, the major dietary monosaccharide.

Starch is actually "poly-glucose" and its hydrolysis in the small intestine yields only glucose. "Sugar", which is table sugar or sucrose, is 50 % glucose and 50 % fructose. Lactose (milk sugar) and HFCS or high fructose corn syrup also contain 50 % glucose. Glucose is that monosaccharide upon which nature has based our metabolism. It serves several differing functions in our tissues. It is the only substrate for anaerobic metabolism (fast, intense exercise), it is one of several substrates for aerobic metabolism (slow, maintained work), is used to build up carbohydrate reserves (as glycogen) and, finally, is a signal substance for control of hormone secretion and appetite control. Glucose metabolism is initiated by either hexokinase or glucokinase. The former is involved in energy metabolism in most tissues and is feed-back controlled. That is, glucose transport into the cell and hexokinase activity rise and fall according to the use of its product, glucose-6-phosphate (G-6-P). Hexokinase has a low K_m for glucose; it can be active at all normal blood glucose concentrations. In other words, the activity of hexokinase is coupled to the substrate requirement of the moment. Additionally, in muscle tissue, hexokinase is linked to storage of glucose as glycogen for later use in anaerobic and aerobic glycolysis.



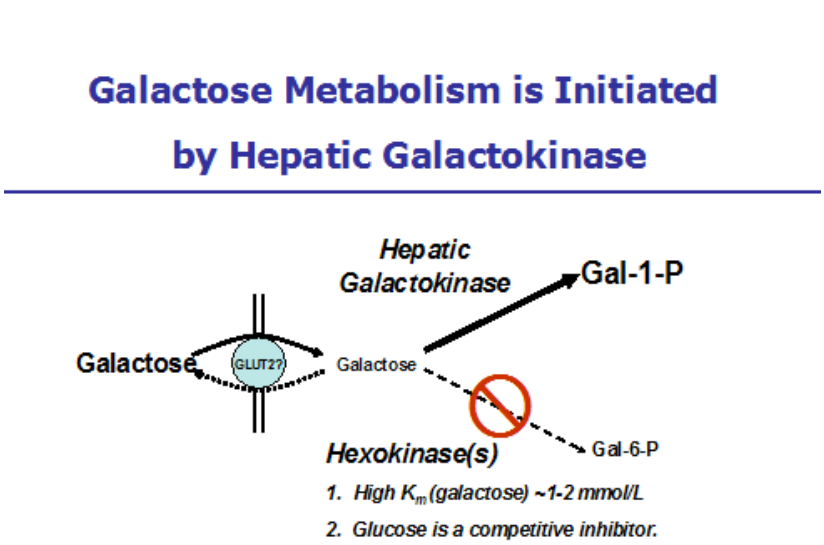
In contrast to hexokinase, glucokinase has a K_m of about 5 mmolar. This is equivalent to normal blood glucose levels. Glucokinase is found in just a few tissues, the liver, ß-cells in the pancreas and in the hypothalamus. Uptake of glucose after a meal can increase the concentration of glucose in portal blood from the normal fasting level of 4-5 mmolar to 20 mmolar or even higher. This activates inward hepatic glucose transport and glucokinase activity. Since glucokinase is not product-inhibited, the liver is able to take up and store large amounts of glucose as glycogen after a meal. This can then be released to the circulation later to stabilize blood glucose levels.

Pancreatic ß-cells secrete insulin in response to very small increases in blood glucose concentration. The glucose transport protein in these cells (GLUT2) and glucokinase both have K_m values of about 5 mmolar. This appears to be also the case for glucokinase-containing cells in the hypothalamus. The couple GLUT2-glucokinase in these cells acts as a glucose sensor, controlling both insulin secretion and appetite. Glucokinase activity automatically rises and falls in tact with changes in glucose concentration in the ß-cell.

Most organs exhibit hexokinase activity. As the name implies, this enzyme is relatively nonspecific and can react with most 6-carbon sugars. However, because of its low affinity for fructose and galactose (K_m = 1.5 mmolar) and the strong competitive inhibitory action of glucose at normal blood glucose concentrations, hexokinase reacts only with glucose in the body's tissues. Glucokinase is specific for glucose and does not catalyze reactions with other sugars.

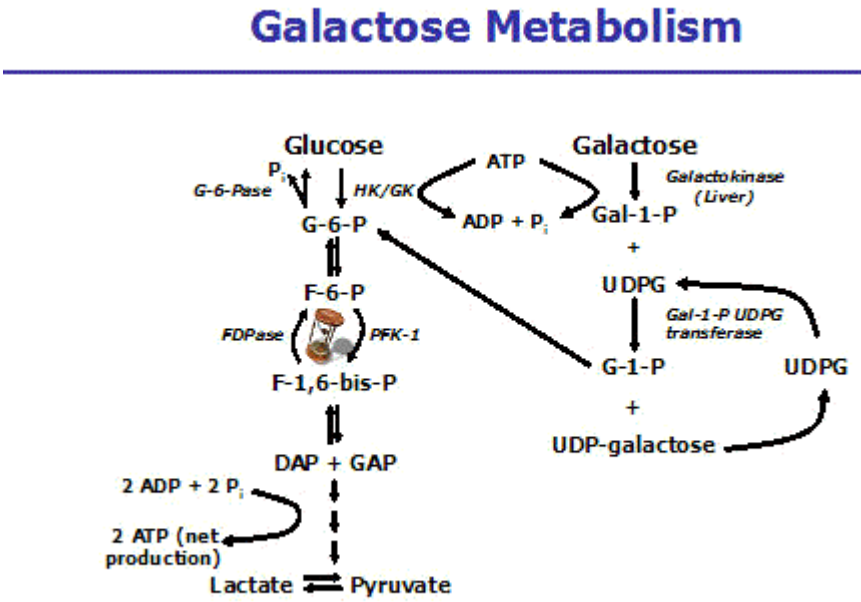
Galactose, the "other half" of lactose (milk sugar).

Galactose is transported from the intestinal lumen by the same Na^+-dependent symport that is responsible for glucose transport. It is then taken up by the liver and phosphorylated by a specific enzyme, galactokinase. The enzymes required for galactose metabolism are found in many tissues including erythrocytes, leucocytes, the brain and retina. However, the liver is the main organ where active metabolism of galactose normally occurs. Galactose is absorbed in the small intestine and transported to the liver via the vena porta. The very active hepatic galactose metabolizing system ((galactokinase (GALK), galactose-1-phosphate uridyltransferase (GALT) and uridine diphosphate galactose-4-epimerase (GALE))) almost completely removes galactose from the circulation. Galactose metabolism is, in practice, normally limited to this organ.



Hexokinase, which might be thought to convert galactose to gal-6-P has a high K_m for galactose. This follows the positioning of the hydroxyl group on carbon four. This is on the same side of the ring as carbon-6 and hinders phosphorylation of the hydroxyl group at this carbon. Galactokinase has high affinity for galactose and catalyzes phosphorylation of the hydroxyl group on carbon-1.

Galactose-1-P is then converted to glucose-1-phosphate by phosphoglucomutase and enters the "normal" glycolytic path. This process is rather complex. It involves exchanging a glucose-1-phosphate group in uridine diphosphate glucose (UDP-glucose) with galactose-1-P. The resulting uridine diphosphate galactose (UDP-galactose) is then converted by an isomerase back to UDP-glucose. Galactose is a good substrate for synthesis of glucose and for anaerobic and aerobic glycolysis. As is the case with glucose, anaerobic glycolysis with galactose as substrate yields two ATPs per sugar.



Galactosemia.

Galactosemia is a condition seen in around 1 of 40-50000 of newly born children. These children possess intestinal lactase activity and can split lactose and take up the liberated galactose and glucose. However, they lack effective hepatic galactose sequestering and metabolism. This follows a genetically determined lack of either hepatic galactosyl uridylyltransferase (classical galactosemia) or galactokinase (non-classical galactosemia.

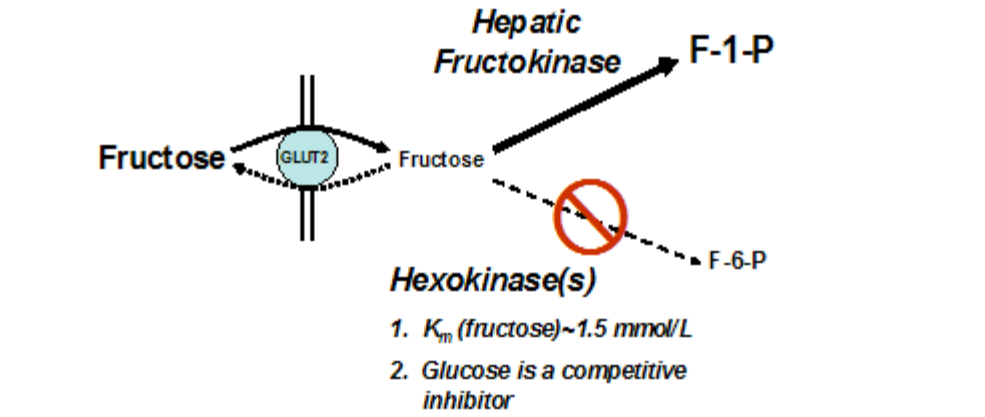
These metabolic "errors" to reduction in blood glucose levels given that half of the sugar in the diet (half of the lactose in milk) is not metabolized. Even more threatening is the trapping of inorganic phosphate as Gal-1-P in classical galactosemia. This depletes hepatic inorganic phosphate and results in a reduction of ATP synthesis. An adequate supply of ATP is essential for gluconeogenesis. Thus, in classical galactosemia, the supply of sugar from the diet is limited and hepatic synthesis of glucose is reduced. The resulting fall in blood glucose can quickly lead to permanent brain damage.

Impaired hepatic galactose metabolism (galactosemia) leads to high circulating levels of galactose. These then serve as substrates for alternative pathways of galactose metabolism. Aldose reductase, found in the eye, converts galactose to galactitol. As is the case with sorbitol formed from glucose, this reduced sugar is not transported over cell membranes. Galactitol and sorbitol therefore accumulate in the lens, leading to increased osmotic pressure, protein denaturation and cataract formation.

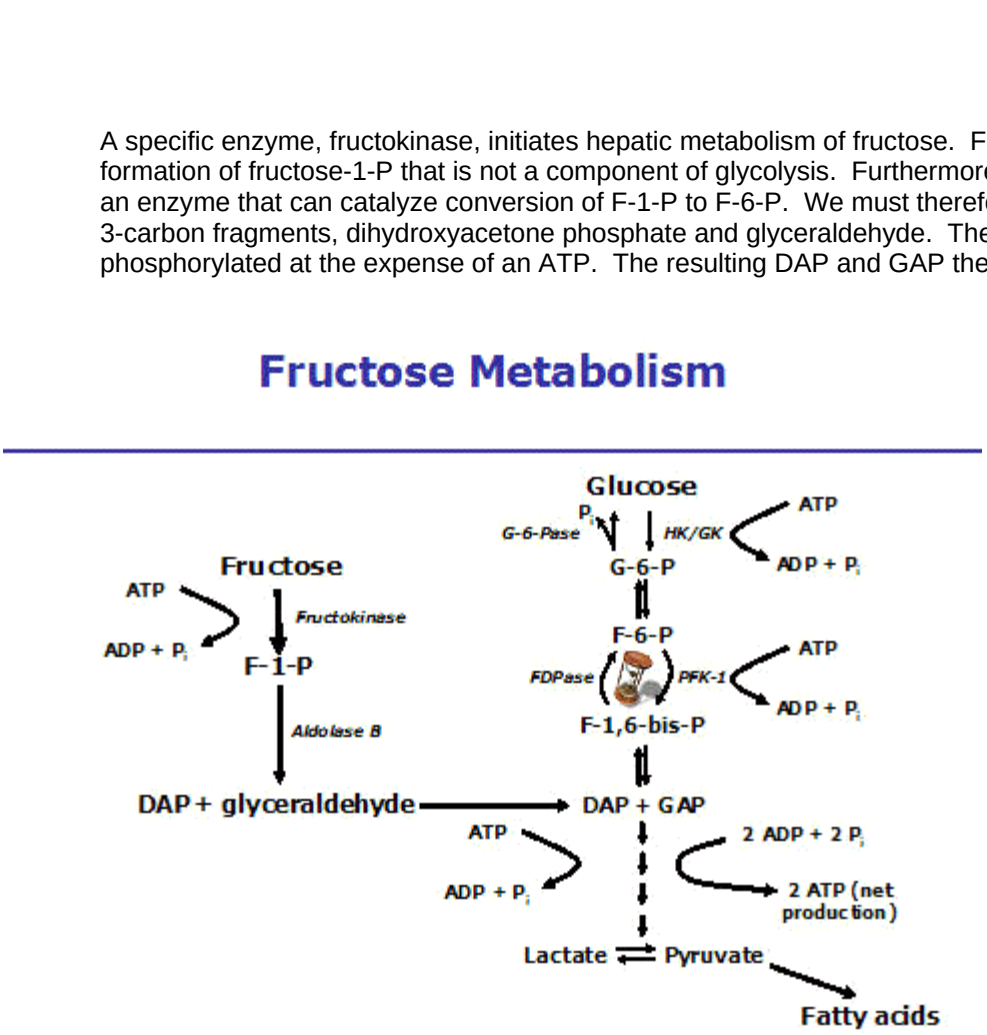
For informative review articles concerning galactose metabolism click here (Galactokinase: structure, function and role in type II galactosemia, H. M. Holden et al, Cell. Mol: Life Sci 61 (2004) 2471-2484) or here (Galactosemia: The Good, the Bad, and the Unknown, J. L. Fridovich-Keil, J. Cell. Physiol. (2006) 701-705).

Fructose or fruit sugar.

Fructose is found in most fruits (~5-6 %), honey (30-40 %) and in "table sugar" or sucrose (50 %). Fructose differs from glucose in that the double-bonded oxygen is found on carbon-2. This results in formation of a 5-ring (furanose) in aqueous solution at room temperature and the formation of a 6-ring (pyranose) at higher temperatures. The 5-ring form is sweeter than common sugar while the 6-ring is not. Fructose has a three-dimensional structure quite unlike glucose. (Click here for the 3D drawings of the common monosaccharides). Hexokinase has a much lower affinity for fructose than glucose (Km ~1.5 mmolar). In most tissues, hexokinase does not catalyze metabolism of fructose since glucose is a strong competitive inhibitor and is found at higher concentrations than fructose. The only exception to this is spermatozoa; seminal fluid contains enough fructose to activate hexokinase.



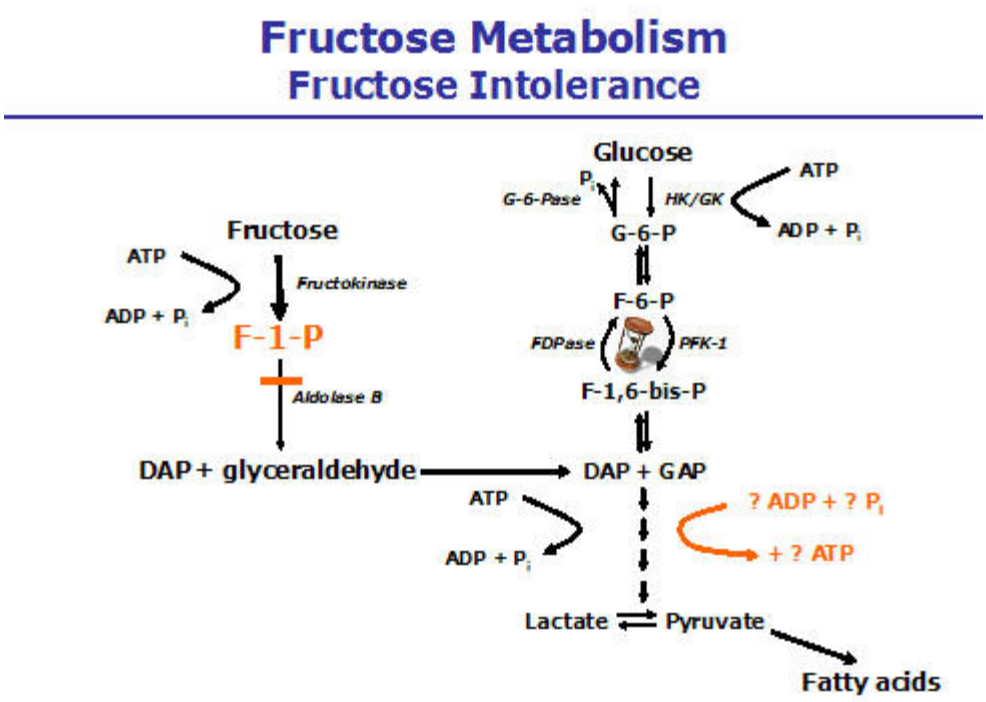
A specific enzyme, fructokinase, initiates hepatic metabolism of fructose. Fructokinase promotes formation of fructose-1-P that is not a component of glycolysis. Furthermore, we do not possess an enzyme that can catalyze conversion of F-1-P to F-6-P. We must therefore split F-1-P into two 3-carbon fragments, dihydroxyacetone phosphate and glyceraldehyde. The latter is then phosphorylated at the expense of an ATP. The resulting DAP and GAP then enters glycolysis and can, in theory, enter gluconeogenesis or aerobic glycolysis. For this reason, fructose has often been suggested as a treatment for hypoglycemia. There are several good reasons to discourage this. Firstly, conversion of fructose to glucose uses 2 ATPs. Normal hepatic activity alone utilizes all of the liver's ATP-synthesizing capacity. There is no good reason to increase hepatic ATP utilization. One can just give common sugar in the form of juice or soda pop instead of fructose. Glucose (also called dextrose) can be given intravenously too.



<u>Fructose is not a direct energy source for muscles and the brain as many of its producers claim.</u> These tissues rely on the hexokinase catalyzed phosphorylation of glucose for energy metabolism. They do not take up fructose from the circulation since they lack both fructokinase and GLUT2. Fructose does increase hepatic fatty acid production and serum lipids and these can be utilized in muscle. However, dyslipidemia is not a desirable situation. Sorry, but you do not become stronger and smarter by eating fructose.

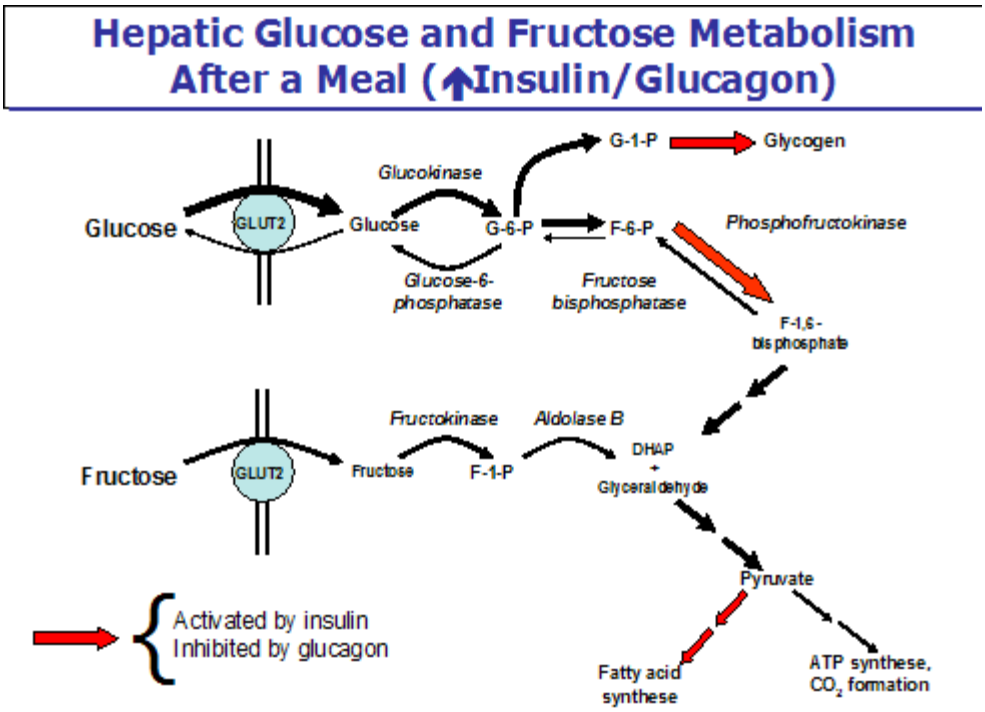
Fructose intolerance.

The human liver has a very large capacity for phosphorylation of fructose. In fact, the fructokinase activity is usually more than twice that of the combined hexokinase and glucokinase activities. Therefore, formation of F-1-P often exceeds the capacity of aldolase B and F-1-P levels can increase after meals. These are then reduced between meals. While F-1-P can act as a trap for P_i , this is usually not a problem for healthy persons. However, individuals with an aldolase B deficiency exhibit so-called fructose intolerance. That is, they build up large amounts of F-1-P following fructose intake and their capacity for hepatic ATP synthesis becomes compromised by the resulting low P_i levels. This resembles the situation in classical galactosemia described above.



Fructose and normal physiology.

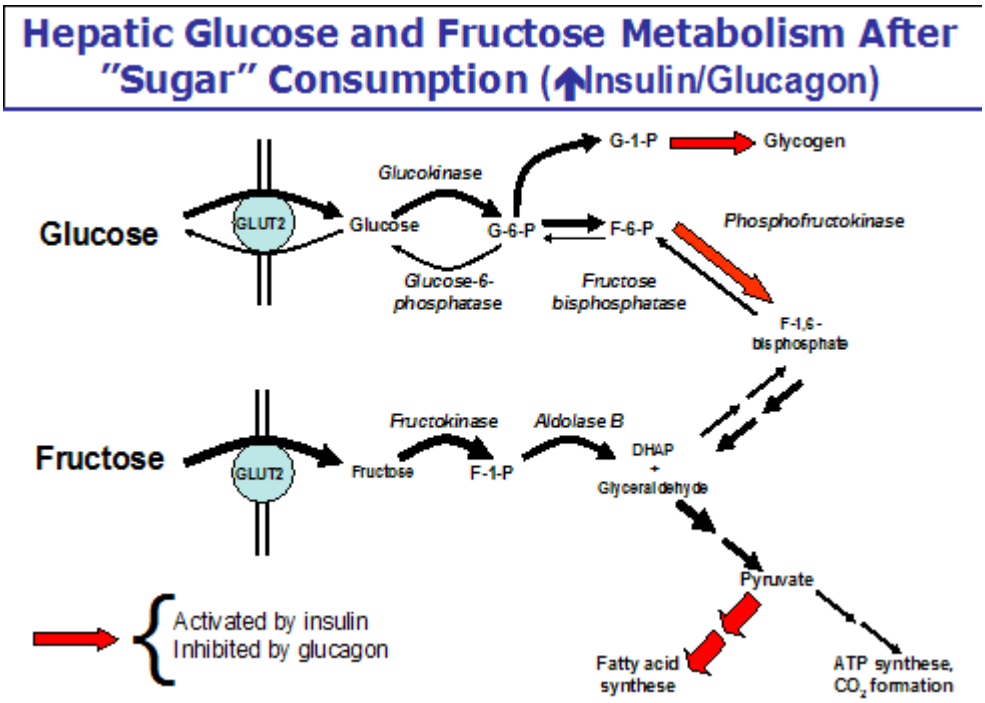
Now, the fact is that we do not usually eat pure fructose. After all, fructose is usually just a part of the sweeteners we use to season our food. The normal hormonal responses we experience from eating and fasting are actual also when we take in a meal containing sugar or fructose.



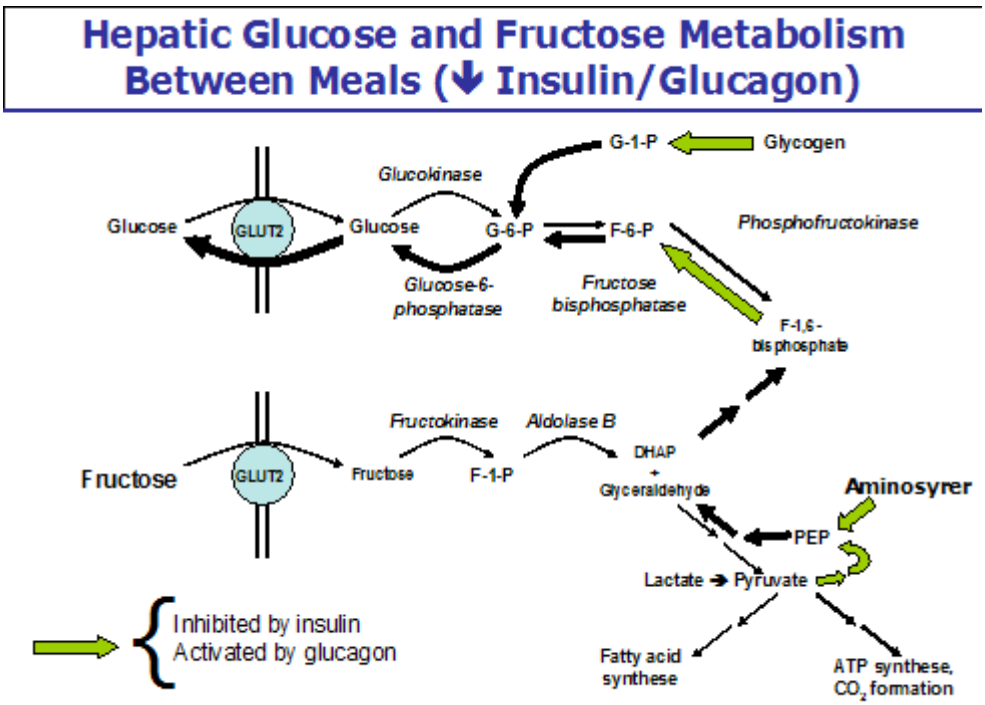
Eating increases insulin secretion and reduces glucagon release; fasting reduces insulin release and stimulates glucagon secretion. These two hormones are the major determinates of hepatic energy metabolism. Look at the figure to the left. This depicts the situation in the liver after a meal with a little fruit, that is, food with normal levels of glucose and fructose. We know that the increased insulin/glucagon ratio that follows a meal increases glycogen synthesis as well as anaerobic and aerobic glycolysis. If there is carbohydrate in excess this will be converted to fatty acids and sent out of the liver in VLDL particles. Note that the balance between glycolysis and gluconeogenesis is shifted toward the former; we do not produce glucose while there is an excess in the circulation. It is only in untreated diabetes that gluconeogenesis proceeds while blood glucose levels are high.

One might think that fructose could be converted to glucose and stored as glycogen. This has been suggested many times by health faddists. However, the balance of insulin and glucagon after a meal rules this out. Gluconeogenesis is turned off, glycolysis races forward and fructose is converted to fatty acids. This is the most likely explanation for the increased triglyceride levels found after in people who use "normal amounts" of sugar. Sugar consumption has increased from about 8 kg/year to over 50 kg/year in many societies during the past 150 years. Genetically, we are designed to consume far less! Today's "normal" sugar consumption is, genetically seen, far from a normal sugar intake.

Let us look at hepatic metabolism after a meal rich in sugar regardless of whether we take in sucrose or replace some of that with fructose. For example a nice piece of pie and a Cola on the side. Perhaps a candy bar just before? Once again, glycogen is synthesized until storage is maximized, gluconeogenesis is turned more or less off, and fatty acid formation is very active.



The only metabolic pathway open to fructose is that which ends up in fatty acid production. And remember, excessive fatty acid and triglyceride levels are convincingly tied to development of the metabolic syndrome, hypertension, glucose intolerance and type 2 diabetes.

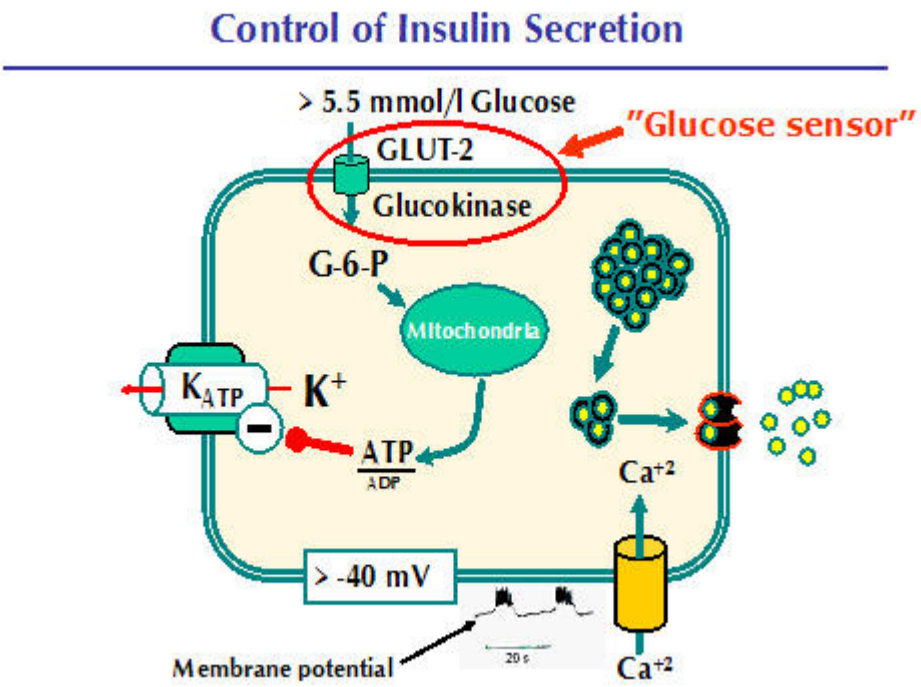


Can fructose be converted to glucose or "blood sugar"? Clearly, the metabolic pathway from fructose to glucose supports this. But does this occur normally? We can look at fructose and

glucose metabolism between meals to gain insight here. The reduced insulin/glucagon ratio stimulates gluconeogenesis and inhibits glycolysis. That is, glucagon dominates the picture, increasing fructose bisphosphatase activity and leading to formation of glucose, mainly from amino acids, lactate and pyruvate. We have no form for fructose reserve; hence fructose is not a usual substrate for gluconeogenesis. However, if one was to drink a pure fructose test drink one would certainly find conversion of that fructose to glucose. However, the more usual situation is consumption of fructose as sugar as a sweetener in a "normal" meal. In other words, we eat fructose together with starch or sugar. This leads to increases in blood sugar and insulin levels directly with a rapid cessation of gluconeogenesis. We do not usually consume pure fructose!

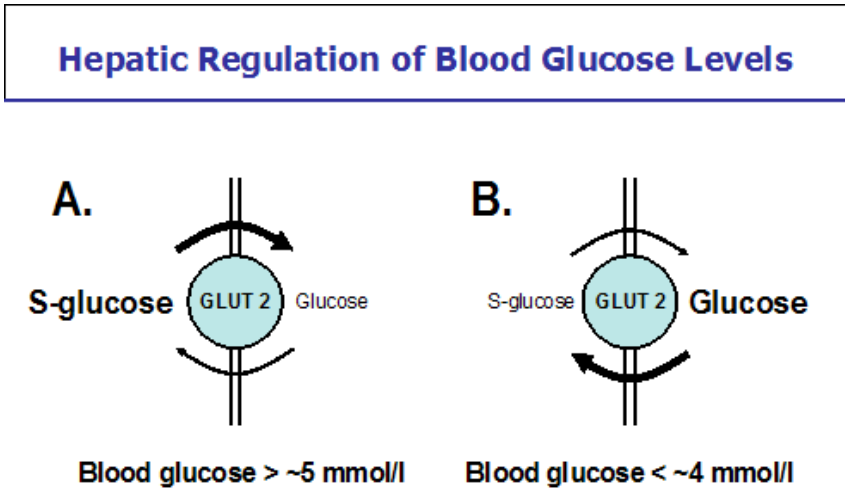
Fructose does not stimulate insulin secretion.

Now, appetite is partially controlled by central effects of insulin. What about fructose as a signal for insulin secretion? Insulin secretion from the pancreatic ß-cells is stimulated by glucose and amino acids and, to a lesser degree, by fatty acids. The coupling point between release of insulin and blood sugar levels is the GLUT2-glucokinase "radar pair". While GLUT2 in the pancreas may perhaps transport fructose, there is no appreciable fructokinase activity in this tissue. Therefore, fructose does not serve as a substrate for ATP synthesis and does not influence ion transport and the membrane potential in ß-cells. <u>Fructose does not stimulate release of insulin!</u> One of insulin's important functions is central regulation of hunger. Fructose does not affect the hypothalamus directly or through insulin. Fructose does not appear to dampen our sense of hunger. Is this why we can drink so much soda pop without losing our appetite?

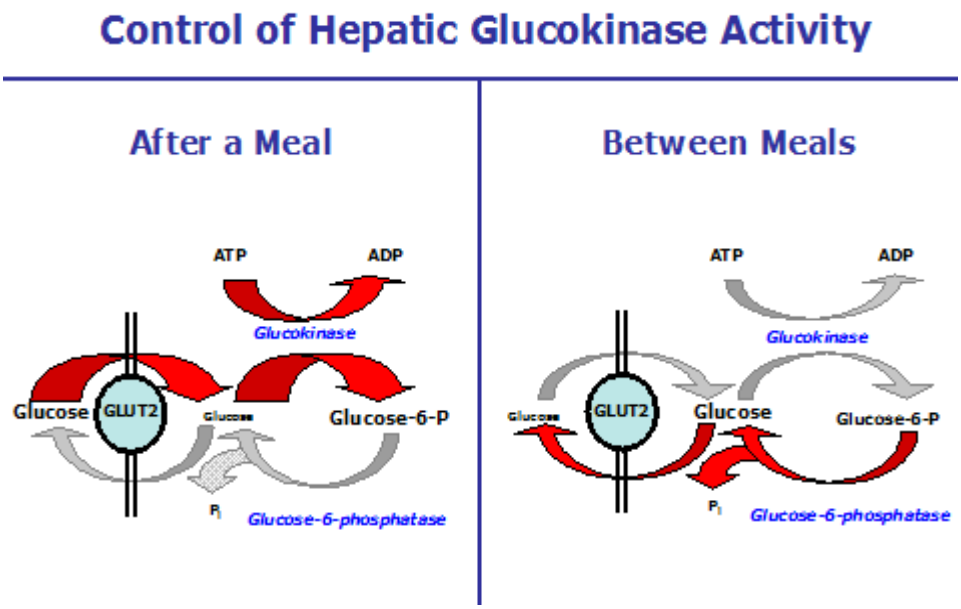


Hepatic glucose release and glucokinase.

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 5-6 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 it must be "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. This leads to an increased concentration of glucose in the liver, and transport via GLUT2 out of the tissue and to the circulation.



It is essential that glucokinase does not become activated and transform glucose to G-6-P during this export process. The balance between glucokinase and glucose-6-phosphatase slides back and forth, increasing uptake to the liver and phosphorylation when the level of blood glucose is high, and releasing glucose from G-6-P when blood glucose falls. This is depicted in the next figure.



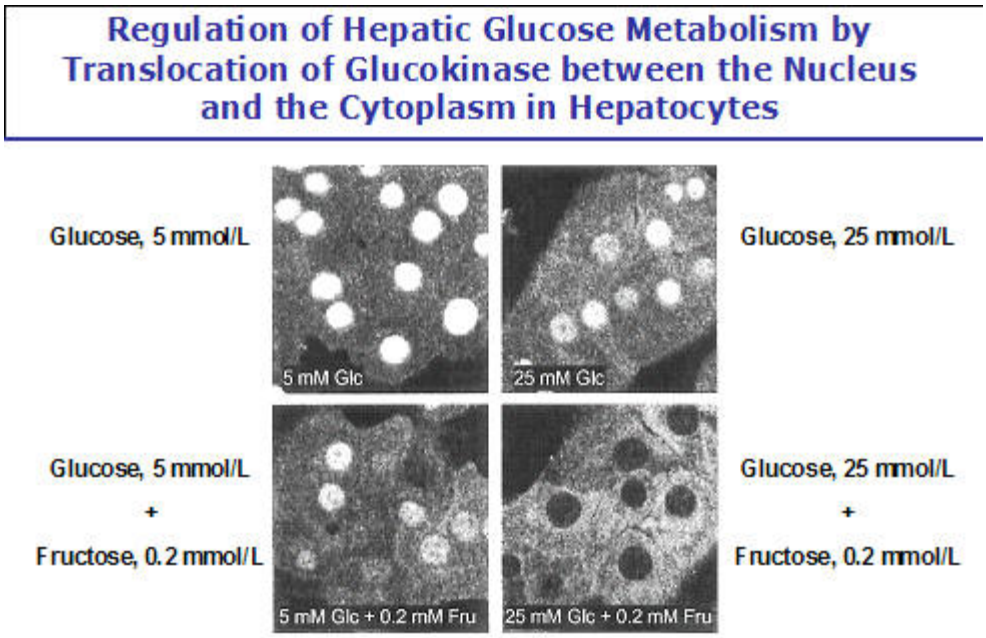
Control of glucose-6-phosphatase activity appears to be largely a function of enzyme concentration, that is, regulation of the genes responsible for synthesis of the enzyme. The minute-to-minute control of the system is thought to lie in regulation of glucokinase activity. As in several other metabolic systems, this concurrent activity of two opposing enzymes leads to "futile cycling". While this "wastes energy", it results in precise control over the system. Well, we need to keep warm and energy "spills" do contribute to this. Just how is glucokinase regulated? It does not possess the "feedback" regulation we have noted for hexokinase.

Earlier, it was thought that glucokinase was rapidly destroyed at low glucose levels and that it was rapidly resynthesised when glucose levels increased. We now know that a much more refined mechanism controls glucokinase activity.

Translocation of glucokinase between cytosol and nucleus.

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! This is the basis for insulin's control of GLUT4 and glucose transport in skeletal muscle and adipose tissue.

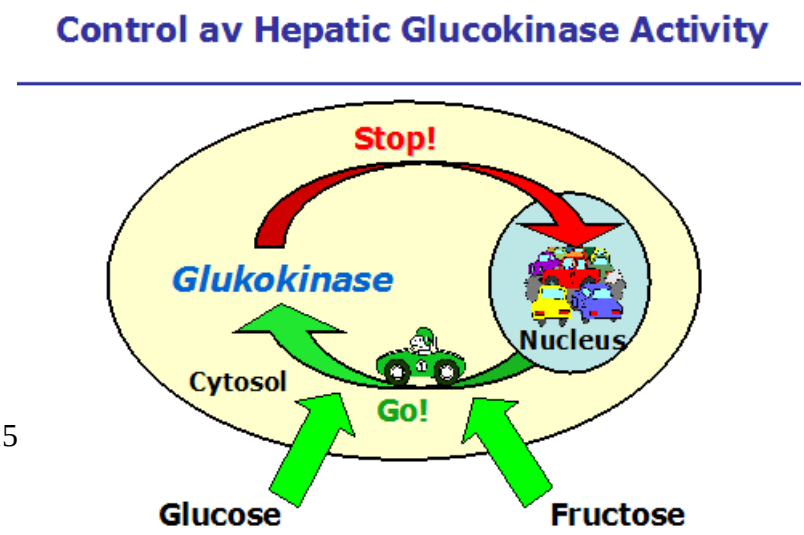
Several publications during the past few years have shown that glucokinase is translocated to the liver cell's nucleus when plasma glucose concentrations approach fasting levels (around 5mmoles/l). It is bound there to a glucokinase regulatory protein called GKRP. Release and translocation back to the cytosol is stimulated by increases in plasma glucose, trace amounts of



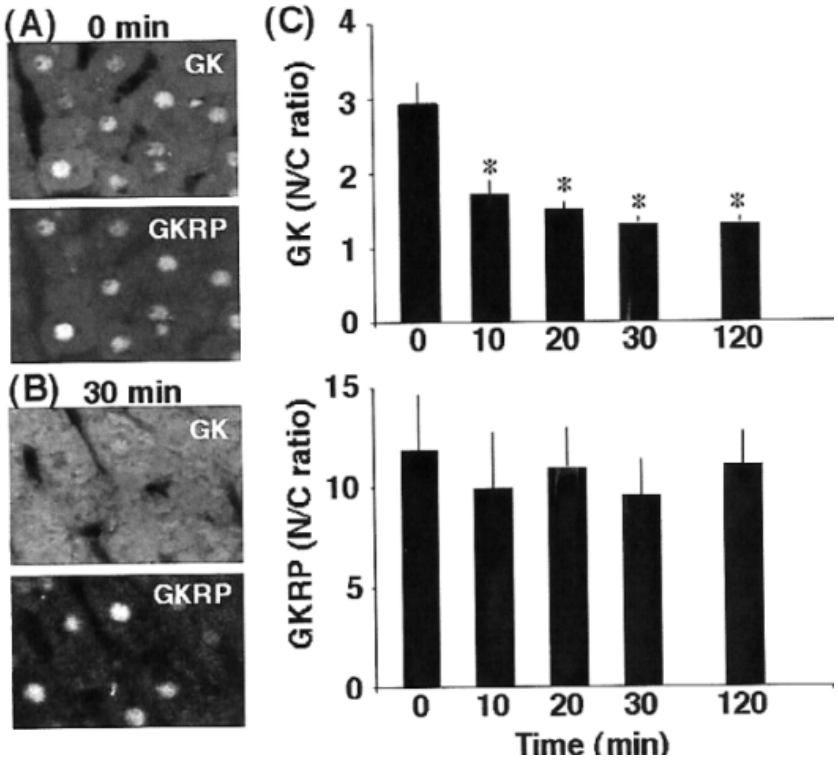
fructose, and insulin. This translocation system is important in directing glucose flow in and out of the hepatocyte. The following figure is taken from "Regulation of Hepatic Glucose Metabolism by Translocation of Glucokinase between the Nucleus and the Cytoplasm in Hepatocytes", Y. Toyoda *et. al.,* Horm Metab Res 33, 329-336 (2001). The bright areas in the pictures are immunofluoresent areas in hepatocytes in culture. The fluorescence comes from a material that binds specifically to 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. Surprisingly, small but naturely occurring amounts of fructose greatly promote this transfer. Is this the reason for the genetic selection of high hepatic fructokinase acticvity?

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 cytosol in the presence of 25 mM glucose. The GK-GKRP complex was previously shown to disassociate in the presence of fructose-1-phosphate. I believe that these are the first pictures showing a simultaneous translocation from nuclei to the cytosol.

The following cartoon gives a simple expression of this "parking" control mechanism.



The time course of this migration has been recently investigated by Chu *et al*. Look up "Rapid Translocation of Hepatic Glucokinase in Response to Intraduodenal Glucose infusion and Changes in Plasma Glucose and Insulin in Conscious Rats, Am J Physiology (in press 01.04) for details. The next figure, taken from that work with permission from Dr. Shiota, clearly shows that migration from the liver cell's nucleus occurs rapidly and within the time interval required to participate in the observed increases in hepatic glucokinase seen after a meal. While GKRP remained in the nucleus, the GK moved to the cytoplasm following perfusion of fasted rats with glucose. Significant increases were noted after only 10 minutes. This corresponds well with the time course of glucokinase activation in these animals.



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 dyslipidemia.

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. 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 former 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. 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! The rapid metabolism of sugar at today's very large levels appears to be responsible for excessive 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. Measurement of plasma triglyceride levels has shown these to be increased by the chronic ingestion of sugar. There is a reliable correlation between sugar consumption, dyslipidemia and metabolic syndrome.

Fructose in our diet.

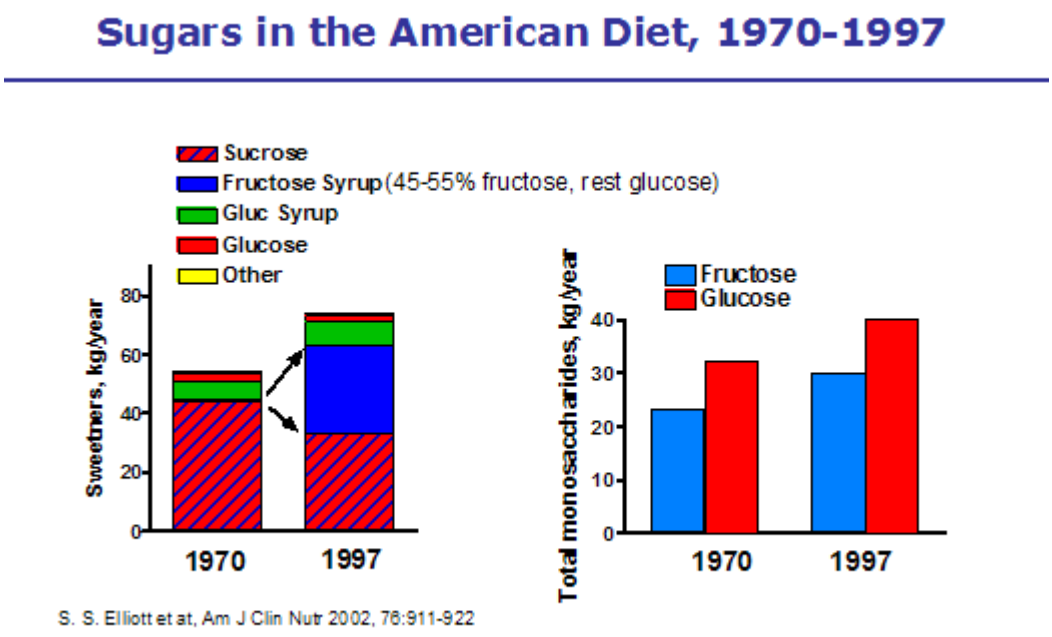
Commercial production of fructose began in Finland in 1969. Since then it has become "modern" to exchange fructose for sugar to cut down on the caloric content of sweetened food. Fructose is sweeter than sucrose. But, it is the 5-ring form of fructose that is sweet, the 6-ring form tastes about the same 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, such that total sugar consumption has markedly increased. Conservative estimates suggest that 16 % of the energy intake of average

Americans comes from fructose. HFCS contains either 42 % or 55 % fructose. It is produced from corn through hydrolysis of starch and isomerisation to fructose. This is then combined with glucose to give an approximately 50:50 blend. The final mixture is less expensive than sucrose. High fructose corn syrup is widely used today in commercial production of soft drinks, breakfast



cereals, baked goods and condiments in the USA.

As we can see from the following figure 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.

The rapid and poorly controlled metabolism of fructose in the liver leads to increased hepatic lipogenesis, dyslipidemia and increased storage of fat in the liver. Increased lipid levels are associated with insulin insensitivity and, therefore, development of metabolic syndrome and type two diabetes. Clearly, today's sucrose and fructose-enriched diets are a threat to health.

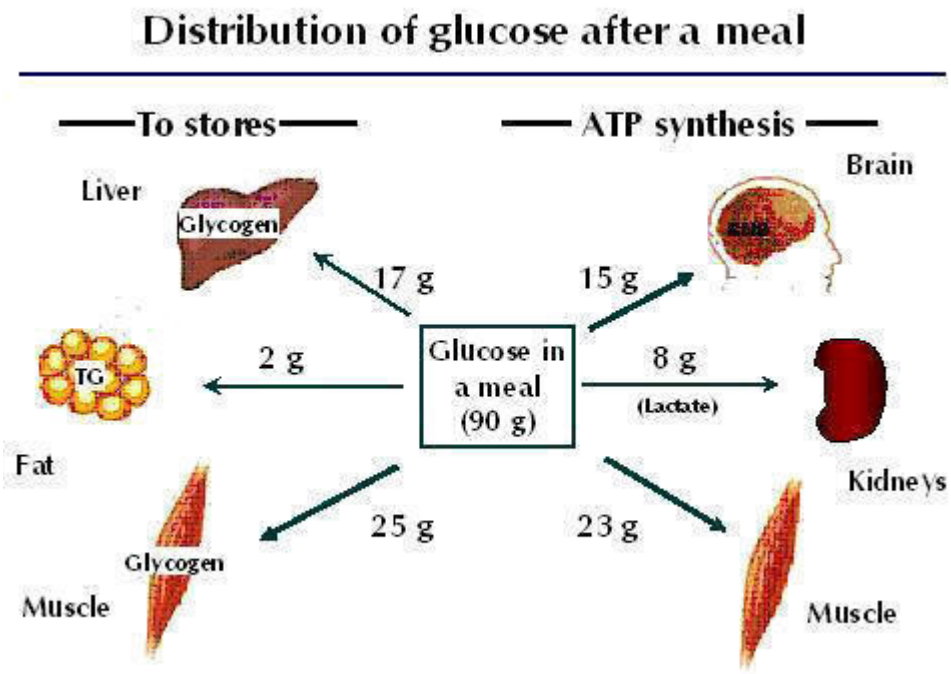
You can read more about fructose, weight gain and insulin resistance in an excellent article by Elliott *et al*, Am J Clin Nutr 76, 911-922 (2002). Just click here if you have access to a library.

Another article which takes up the fructose issue can be found here: ChREBP, a Transcriptional Regulator of Glucose and Lipid Metabolism, C.Postic *et.al*., Annu. Rev. Nutr., 2007. 27:179-192. Click here if you have library connections.

Lactate; some cells make it, others use it.

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 that 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!

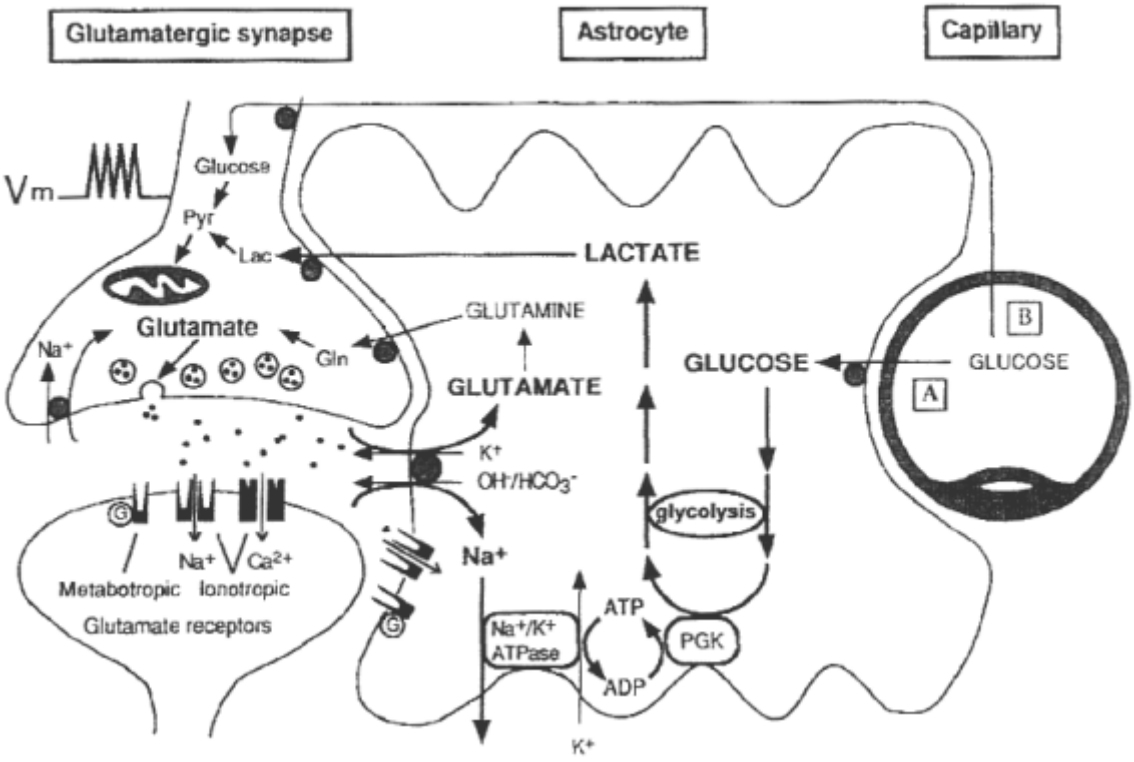


Lactate metabolism in the brain.

We have all learned that the 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. ß-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.