Blood Sugar Levels are Stable

Who has not heard people say "my blood sugar is low, I need a Cola" or something like that. We all "know" that if our blood sugar level falls we feel weak, confused and have difficulty thinking. For some of my students a candy bar or a bottle of soda is almost indispensable to come through an examination!

However, the facts are:

- A stable blood glucose level is absolutely essential for normal brain function. The brain can only use glucose or ketone bodies as its fuel. Ketone bodies (acetyl acetate or ß-hydroxybutyrate) cannot replace glucose as the brain's energy source on short notice. About 10-14 days are required to increase plasma ketone body levels such that they can provide energy for neural tissues. At most they can provide about 50% of the brain's energy, the rest must come from glucose.

- Blood sugar levels are usually between 4.5 to 5.5 mmoles/l and swing about 10-15% around these values. We do not normally experience low blood sugar levels. Hypoglycemia does ram some few people including persons with diabetes who have not eaten after taking insulin, others with insulin-producing tumors, newborn with untreated galactosemia, some alcohol-poisoned people, athletes who exceed their capacity in a competition and others with a variety of liver diseases. For most of us (relatively healthy persons), low blood sugar just does not happen.
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- Most nutritionists recommend a diet in which between 50 and 60 % of the caloric content is contributed by carbohydrates. However, we can exist quite well on diets containing with little or no carbohydrate. Low starch and sugar intake does not reduce blood sugar levels: we maintain normal blood glucose levels in spite of large variations in sugar and starch consumption. The key to this is the ability of both the liver and kidneys to synthesize glucose from amino acids (derived from proteins in the diet or from the body's muscle mass). Loss of control of hepatic glucose production is a major factor in development of the high blood sugar levels seen in type 2 diabetes mellitus.

Energy Stores in Humans.

The surprising part of this business is that we have a very limited amount of circulating glucose in spite of a very rapid and extensive use of this sugar as an

energy source. Look at the table below. The highlighted area shows how long our blood and extracellular glucose can support differing activity levels.

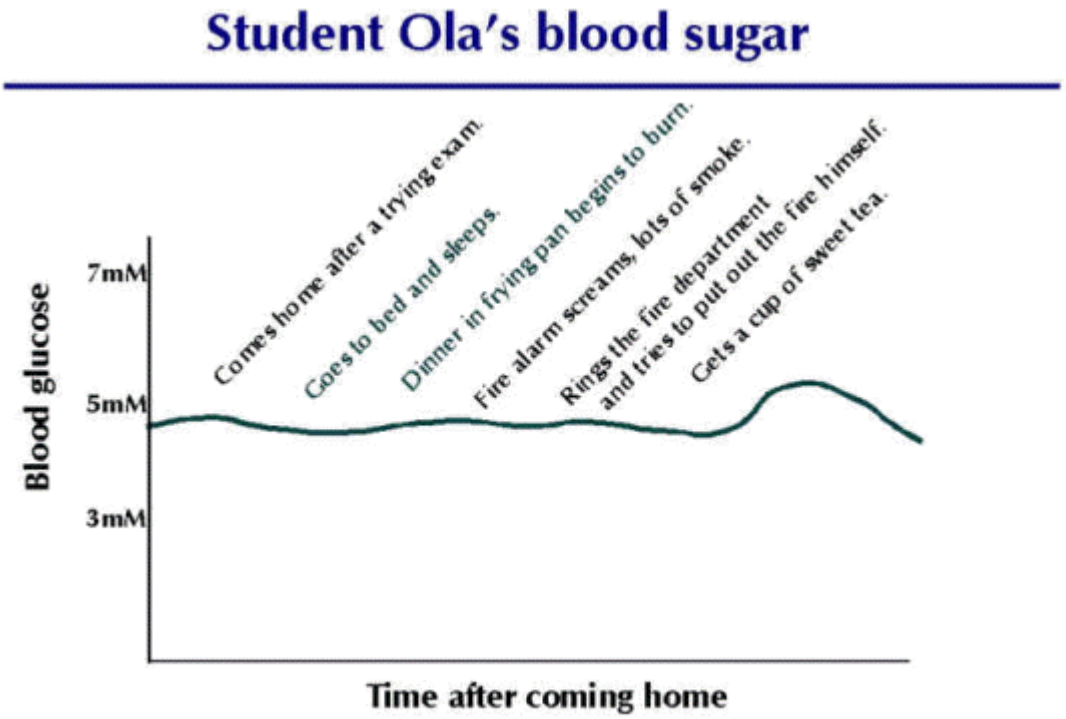
Our total reserve of glucose is around 20 grams of which approximately 5 grams are found in the blood. Twenty grams of glucose give enough energy for about 40 minutes with little or no activity! If you just sit and relax you could use all of your glucose in less than one hour! If you walk, glucose could disappear in around 15 minutes and moderate work (that which can be maintained for some few hours) might exhaust your sugar reserves in about 4 minutes.

Energy Stores in Man				
Tissue Fuel	Provides fuel for			
	Reserve, grams	Starvation	Walking	Marathon
Fat	9000-15000	34 days	11 days	3 days
Muscle Glycogen	350	14 hours	5 hours	70 minutes
Liver Glycogen	80	3.5 hours	70 minutes	18 minutes
Blood/Extracellular Glucose	20	40 minutes	15 minutes	4 minutes
Body Protein	6000	15 days	5 days	1.3 days

Now, these estimates do not take into account that one will faint or go into a coma when the blood sugar is reduced by around 50%, so the real limits in time are about 1/2 of those quoted above. Why? Because the brain can only utilize glucose as an energy source. There is no uptake mechanism for fatty acids in the brain. Ketone bodies can go in as an energy source, but adaptation to starvation and central use of ketone bodies takes almost two weeks. An abrupt fall in blood glucose is as devastating as drowning! But remember that these hypoglycemic catastrophes do not normally occur. Our hepatic glycogen reserves and gluconeogenetic capacity prevent development of low serum glucose levels. Strangely, the system works. We can and do manage very well with only small amounts of blood glucose since liver and kidney glucose production rapidly replaces glucose take up from the circulation.

Here comes an example of just how stable blood glucose is.

A Hard Day or "Blood Sugar in Stress".

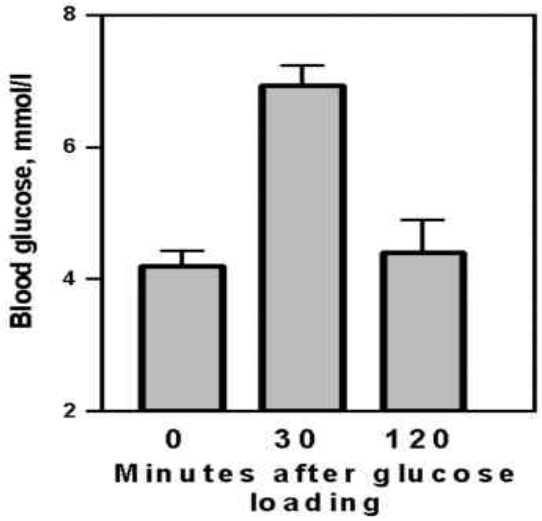


I have no doubt that Ola was both exhausted, dizzy and all that jazz when he came home after a grueling math examination. That he was confused is confirmed by the fact that he threw a few frozen hamburgers in a frying pan and then went to bed. The thing to note here are his blood glucose values. Despite his fatigue, the stress of almost burning down his apartment, fire-fighting and what not, his blood sugar remained relatively constant. The only real change came when he drank a cup of sweet tea. Even here, we see a return to normal glucose values after a short time.

Once again, blood sugar levels in healthy persons do not fall more than 10-15%. We have several mechanisms that are very effective in replacing blood glucose almost as soon as its levels falls.

A Student Exercise: The Glucose Tolerance Test.

We have a student experiment that is offered to first-year medical students. This is actually a clinical test (glucose tolerance test), used to determine a patient's ability to secrete insulin and maintain normal blood glucose levels after a glucose load. The students fast overnight, come to the University and take part in the morning's teaching. They then measure their blood sugar level 10-14 hours following their last meal, drink a glucose mixture containing 75 grams of glucose and determine blood glucose levels after 30 and 120 minutes. Here is a set of typical results. You can see that despite the long fasting period and the stress of coming to the University and participating in classes, they still had a normal blood sugar level at the start of the experiment. Thirty minutes after drinking the sugar solution they had blood glucose levels of approximately around 7 mmol/l. Two hours after the glucose loading the student's blood sugar had reached a normal resting level.



Conclusions:

- Overnight fasting and light work do not normally reduce blood sugar levels below normal levels.
- Consumption of a large sugar load leads to increases in blood glucose, but these are kept below those that lead to appearance of glucose in urine.
- Normal levels are again reached within 2 hours after ingestion of a glucose load.

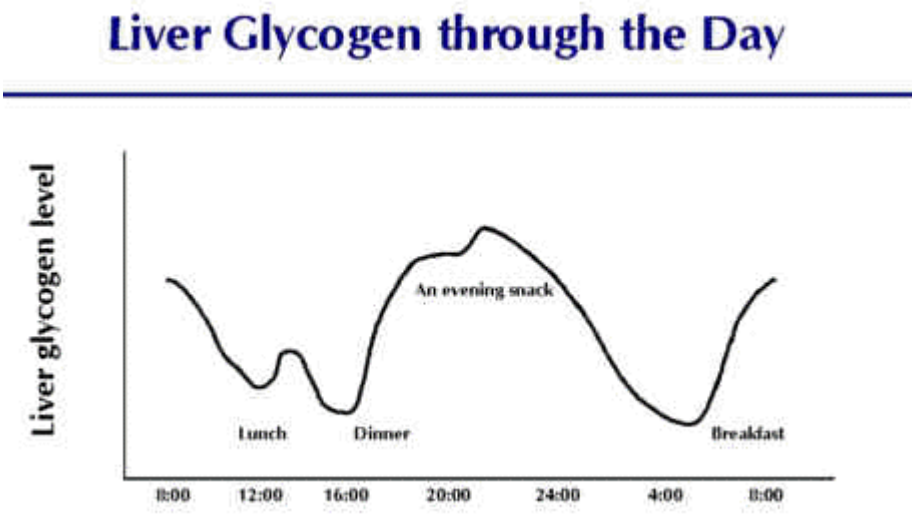
The Bottom Line.

- Blood sugar is quite stable under most physiological conditions in healthy people regardless of their activity level. The only normal exception is the increase seen after meals.
- There must be powerful and sensitive mechanisms to control and stabilize blood sugar levels. This is absolutely essential for the brain's metabolism as

it cannot take up other nutrients from the blood stream. There is, however, the exception of ketone bodies as I have already mentioned. At best these account for about 50% of the brain's energy supply.

Sources of Blood Glucose.

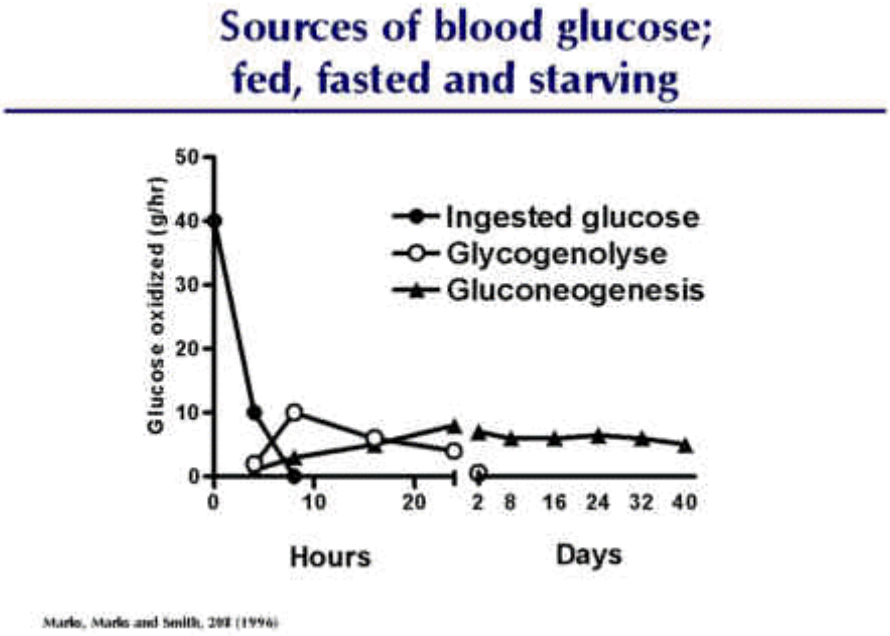
The first line of defense against a fall in blood glucose is the liver's glycogen reserve. This polysaccharide can be rapidly split into glucose units which are then transported to the blood. Indeed, this is the only major function of liver glycogen. It is not utilized by the liver to support its own requirements for energy.



Look at the curve to the left. This gives an picture of the normal fluctuations in liver glycogen levels throughout the day. (Note that the curve starts and ends at 8:00 AM).

Liver glycogen levels fall dramatically during the night. We wake up with little or no glycogen reserves. The day should begin with a breakfast that includes carbohydrates. The glucose from these replaces the glycogen that is used while we sleep. Liver glycogen falls thereafter, supporting blood glucose levels during the morning's activities. A new increase in hepatic glycogen follows lunch, and a major climb is seen after a "good dinner" and an evening snack. Then comes the long dark night and glycogen levels fall once more to rather low levels.

What if you do not "listen to Mom" and skip breakfast? Well, your blood glucose will probably be just as stable as after a good meal, but the mechanism for this will be quite different. Instead of a hormone balance dominated by insulin and synthetic



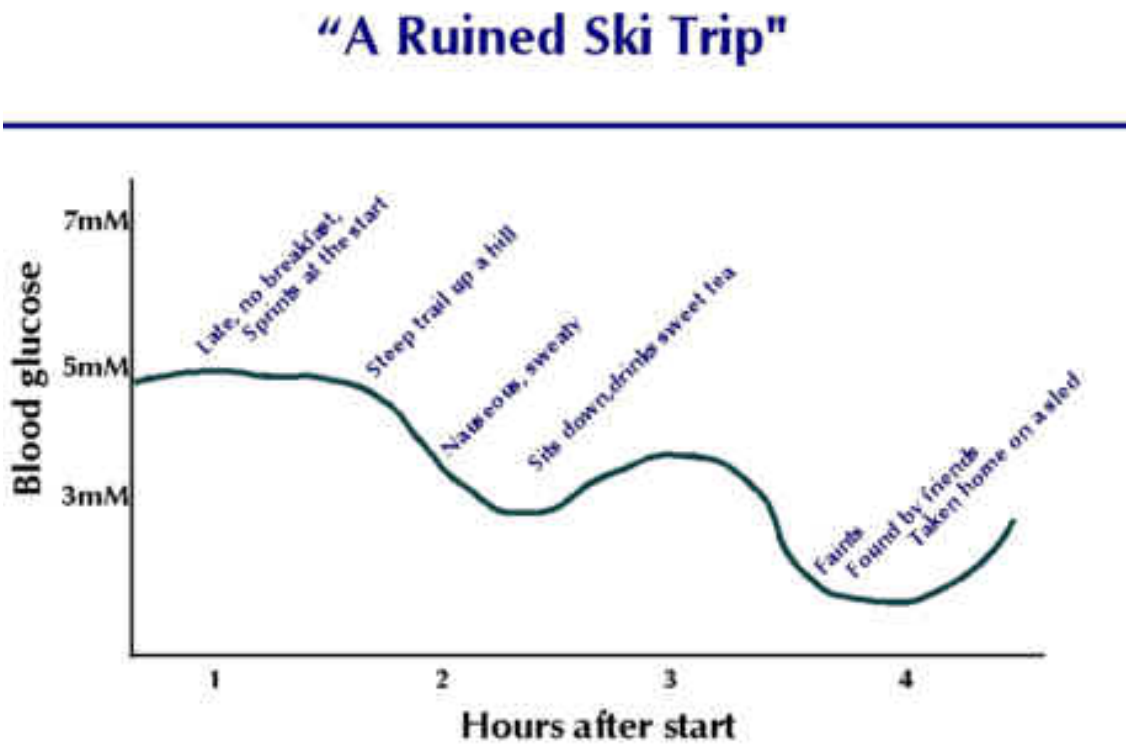
processes, skipping breakfast forces the body to call forward the stress hormones glucagon, adrenaline and growth hormone. These rearrange metabolism such that lactate and amino acids are converted by the liver to glucose, so-called gluconeogenesis. We see that gluconeogenesis is quite active after about 10-12 hours after the last meal. This may be a useful solution to keep blood sugar stable, but the stress hormone response does not lead to an ideal setting for learning or contemplative work.

Gluconeogenesis can provide enough glucose for moderate energy utilization for some weeks, using amino acids derived from muscles as substrate.

Low blood glucose levels can and do occur. Here is an example of a situation leading to hypoglycemia.

Hypoglycemia: Hard Work, No Food...

Hard physical work and fasting is an unbeatable combination to lower blood glucose abruptly and lead to loss of consciousness. The mechanism is quite simple. Gluconeogenesis cannot provide enough glucose to support the muscle's requirement for an energy substrate under hard work. We have seen on TV the marathon runner



that winds up lying in a ditch instead of coming to the finish line, skiers who collapse, etc. Why does this happen? Consider the fabricated example that follows. A young man has planned a ski trip but gets up late. Wanting to meet his friends he skipped over breakfast and raced away. At the first steep hill he began to feel unwell, was soon nauseous, sweated and felt faint. He felt better after a short rest and a cup of sweet tea, ran once more as fast as possible and, a little later fainted. Why? Remember the liver glycogen curve shown earlier. We begin the day with low levels of this blood glucose buffer. Without breakfast and restoration of liver glycogen we have only gluconeogenesis to support the level of blood sugar. Hard physical work can increase the energy output (and fuel consumption) of muscle by a factor of 18-20. Increased metabolism within a muscle cell increases the uptake of glucose from with blood without increased insulin levels! The body's muscle mass "steals" glucose from the brain and this can lead to loss of consciousness. This is the same phenomena that diabetes patients experience when they take insulin without eating enough afterward, so called insulin reaction or "feeling" as we say in Norway.

How is the level of blood glucose controlled?

One way to approach an answer to this question is to look at the consequences of changes in blood glucose levels.

Glucose Levels Between Meals:

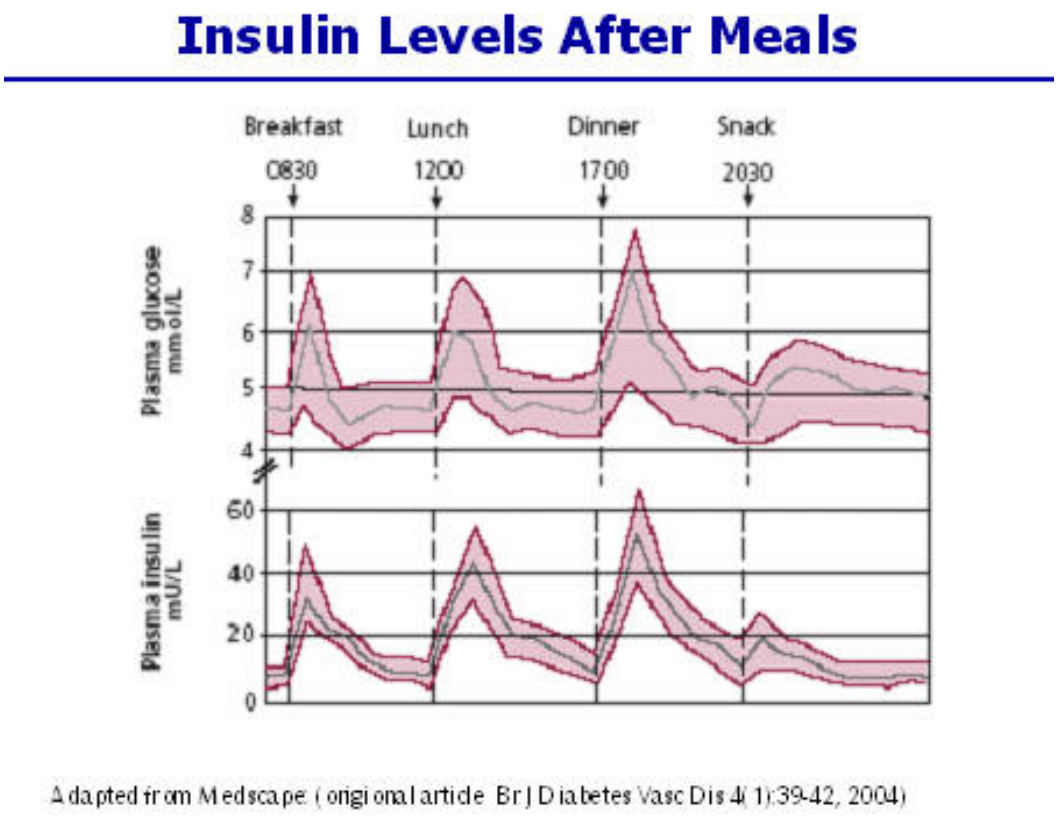
The normal level of blood glucose seen in active people between meals is highlighted in yellow in the table below.

Consequences of hyper and hypoglycemia	
Blood glucose, mmol/l	Result
> 8	Exceeds renal threshold for uptake of glucose from pre-urine, diuresis (loss of glucose, water, $Na^+$and K^+ in urine).
5.5	Insulin secretion increases.
4.6	Insulin secretion decreases.
3.8	Increased secretion of glucagon, adrenaline and growth hormone.
3.2	Cortisol secretion.
2.8	Confusion.
1.7	Weak, sweat, nauseous.
1.1	Muscle cramps.
0.6	Brain damage, death.

At normal fasting glucose levels, slight changes in sugar concentration are counteracted by stimulation or inhibition of insulin release. This results in a strict control of glucose uptake in muscle and adipose tissue and release of glucose from the liver. The balanced actions of insulin and glucagon stabilize blood glucose levels. Pancreatic ß-cells (those responsible for secretion of insulin) are capable of measuring blood glucose concentration and responding quickly to variations in its concentration in blood.

Insulin Levels After Meals.

Insulin levels rise and fall in tact with food consumption as shown in the following figure. Maximal blood concentrations are reached after approximately one hour after a meal. A rapid fall in insulin level follows, reducing uptake of glucose to skeletal muscles and adipose tissue and acting to stabilize blood glucose levels. The figure also shows the relationship between the amount of ingested food and secretion of insulin; large meals lead to higher insulin levels. Anabolic processes such as glycogen, protein and lipid synthesis are enhanced when insulin levels increase. Insulin has CNS effects. A dampening of hunger by insulin has been suggested to be a major factor in regulation of appetite.



Adapted from Medscape (original article Br J Diabetes Vasc Dis 4(1):39-42, 2004)

It has become apparent in recent years that treatment of diabetes type 1 should seek to duplicate the normal blood sugar-blood insulin picture. "Basis-bolus" insulin regimens are now suggested for many patients. Long acting insulin preparations are used to hold a basal level throughout the day and a rapid or short acting insulin injection is used at meal times. Go to the Medscape article if you will learn more about this (click here).

Diabetic Hyperglycemia.

In diabetes, the uptake of glucose in muscle and fat decreases due to a loss of insulin production or to a lack of an adequate response to the hormone. This results in increases in the blood level of glucose. When the concentration of glucose exceeds 8-10 mmol/l, it is lost to the urine. This is due to the inability of the kidneys to reabsorb all of the glucose present in the first filtration product in the kidney (pre-urine) when the glucose concentration exceeds around 10 mmol/l. Diuresis (loss of water due to the osmotic effect of glucose) follows with loss of electrolytes, mainly sodium and potassium. In diabetes type 1 (characterized by destruction of ß-cells), the daily carbohydrate loss can be the equivalent of 2 loaves of bread. Children who develop this disease become extremely thirsty, have to urinate frequently and lose weight rapidly.

Hormones that Increase Blood Glucose Levels.

Hormones that balance insulin's action and that increase blood glucose levels come into play when blood glucose falls to around 3.8 mmol/l. We see that secretion of glucagon, adrenaline and growth hormone are stimulated by falling blood glucose levels. It is important to recognize that there is a constant basal secretion of insulin and glucagon and that it is the molar ratio of these two hormones that directs metabolism. This is like driving a car with one foot on the gas and the other on the brakes. You get a very exact control over the car, but you loose some energy too. Our bodies are designed to obtain maximal control over metabolism, allowing some energy waste that, at the same time, keep us warm.

Glucose Production in Starvation.

Fasting goes over to starvation when the period without food exceeds a day or two. While glucagon, adrenaline and growth hormone promote glycogenolysis and gluconeogenesis, these hormones do not provide the amino acids that are substrates for gluconeogenesis. We need cortisol for this. Cortisol inhibits protein synthesis and shifts the balance between protein anabolism and catabolism, leading to release of amino acids from liver and muscle fibers. One surprising aspect of these actions of cortisol is that, while synthesis of most proteins decreases with increased cortisol, synthesis of enzymes involved in gluconeogenesis increases in the liver. We get a situation where amino acids are released as substrates for glucose formation and increased gluconeogenetic enzyme levels to do that job! We see from the table that cortisol secretion begins at about glucose levels of about 3.2 mmol/l.

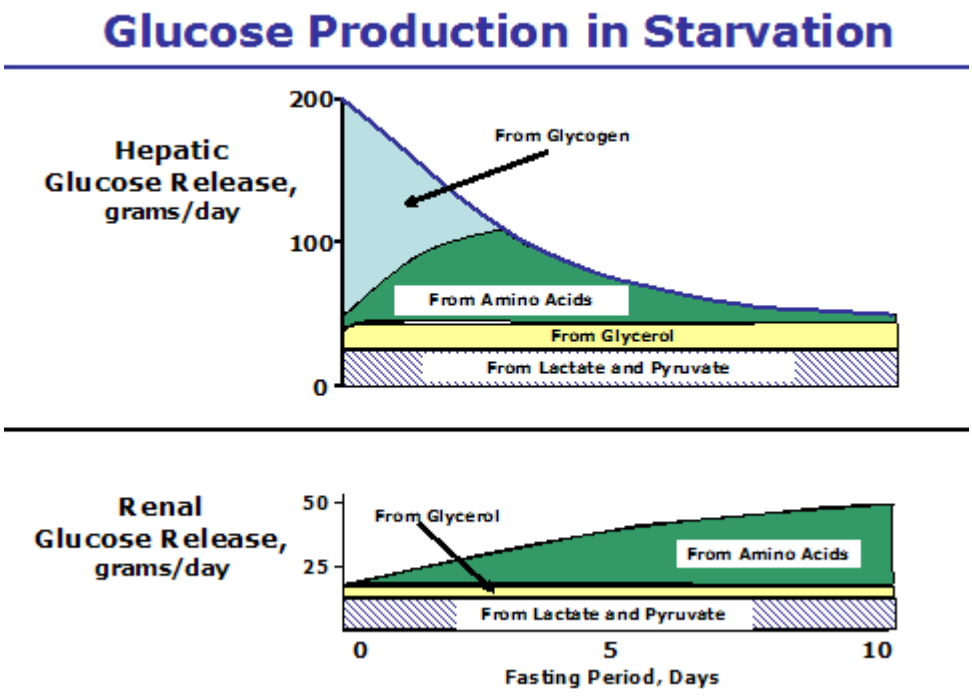
Muscle protein is, by far, the most important source of substrate for gluconeogenesis. The levels of the various muscle proteins are not static, but are determined by the balance between anabolic and catabolic processes. Amino acids are either taken up by or released from muscle tissue according to the body's hormone balance. This is where cortisol comes into the picture. Cortisol acts at the muscle cell nucleus to inhibit the production of many proteins, so that the rate of protein breakdown exceeds the rate of protein synthesis. Thus, increases in circulating cortisol will inhibit protein synthesis in muscle cells and lead to release of

amino acids. Because an active transamination takes place prior to release, we find that alanine and glutamine represent about one half of the total amino acids released from muscle tissue under a long fasting period. Alanine acts as substrate for gluconeogenesis in the liver; glutamate is the substrate of choice for kidney gluconeogenesis.

Both Liver and Kidneys Synthesize Glucose.

The liver and kidneys are the only tissues that can release glucose into the blood stream. These produce glucose-6-phosphatase, an essential enzyme for cleavage of phosphate from G-6-P, the precursor of glucose. While earlier work suggested that only the liver produces glucose, we now know that the kidneys actively support sugar synthesis. You can click on the following reference for more information: J. E. Gerich et. al; Diabetes Care 24, 382-391, 2001.

Let us examine the time-pattern of release of glucose from these organs. Breakdown of hepatic glycogen accounts for a major portion of the glucose released from the liver during the first day of a fast. A relative constant the hepatic gluconeogenesis using glycerol, lactate and pyruvate as substrate occurs throughout the fasting period. Amino acids from both liver and muscle proteins are used as



substrate for gluconeogenesis with peak production from amino acids occurring at about 2-3 days of starvation. The rapid increase in formation of glucose from amino acids in the liver is most likely the result of degradation of hepatic proteins. Amino acids from these are rapidly used as substrate for gluconeogenesis. Alanine from skeletal muscles is also a major contributor to hepatic glucose production. However,

degradation of muscle proteins begins somewhat later than hepatic protein breakdown. Total hepatic glucose production diminishes during the first week of starvation and remains relatively stable at approximately 50 grams/day from day 7 or 8.

Renal production of glucose proceeds mainly from amino acids, increasing gradually from the beginning of the fast and reaching a top at about the same time as hepatic production stabilizes. This reflects "arrival" of amino acids from muscular protein degradation which, as mentioned above, is a slowly initiated process. Glutamine from muscle proteins is a major substrate for gluconeogenesis in the kidney. An active renal glutaminase splits glutamine to glutamate and NH_4^+. Glutamate is then further deaminated and processed through gluconeogenesis. Hepatic and renal gluconeogenesis are approximately equally productive and together give the body around 100 grams of glucose/day. (Please note the differing scales of glucose production in the figure). The liver couples deamination of the amino acids to ureogenesis, an energy-requiring process. This limits the liver's capacity for glucose production. The kidneys get around this constraint by sending NH_4^+ directly into the urine as a counterion for acids. Renal production of glucose exceeds hepatic glucose synthesis per gram tissue.

Control of Hepatic Glucose Production(new Feb. 2007).

The balance between insulin, glucagon and sympathetic nervous system has been thought to control the liver's output of glucose from glycogen and gluconeogenesis. These hormonal elements control glycogen synthesis and breakdown through regulation of glycogen phosphorylase and glycogen synthetase. Major regulation of gluconeogenesis was thought to follow hormonal control of the PFK/FDPase system through control of PFK2 (see any newer biochemistry textbook for details). However, a completely unexpected and extremely striking observation was reported by Mitro et al in Nature 445, 219-223 (2007). Click on the hyperlink to see the original article. These authors clearly demonstrated that LXR, a nuclear hormone receptor, binds glucose and that this interaction regulates synthesis of key enzymes in glucose and lipid synthesis. High physiological levels of glucose inhibit PEPCK synthesis (thereby reducing glucose synthesis) and stimulate energy storage by increasing hepatic lipid production. Thus, an important aspect of control of blood glucose levels is a consequence of direct interaction of the sugar with nuclear regulatory elements leading to management of specific genes and associated enzyme synthesis. The possible relationship between these findings and development of type 2 diabetes is most intriguing!

What limits the liver's capacity to convert amino acids to glucose?

Conversion of amino acids to glucose involves several metabolic processes; deamination or transamination, conversion of the released NH_4^+ to urea and finally synthesis of glucose from amino acid residues. The key to understanding the physiological limitation of glucose formation from amino acids lies in the large amount of energy required to fuel these processes. Energy in the sense used here

means the hydrolysis of adenosinetriphosphate (ATP) to either AMP + PPi or ADP + Pi. Four ATP molecules are used to convert two NH_4^+ to urea and six more are required to convert the carbon skeletons of these amino acids to glucose. One ATP is also required to add a glucosyl group to a glycogen molecule. So, you see, a lot of energy is used in this process. All cells and tissues are built up such that ATP levels are relatively stable. This is a basic prerequisite for life. Under gluconeogenesis the liver must rely upon aerobic metabolism to replace the ATP that is consumed. By definition this is an oxygen-dependent process. The "catch" is that the liver obtains most of its oxygen from the portal vein where the partial pressure of oxygen is rather low. This limits uptake of oxygen, limits ATP production and synthesis of glucose from amino acids.

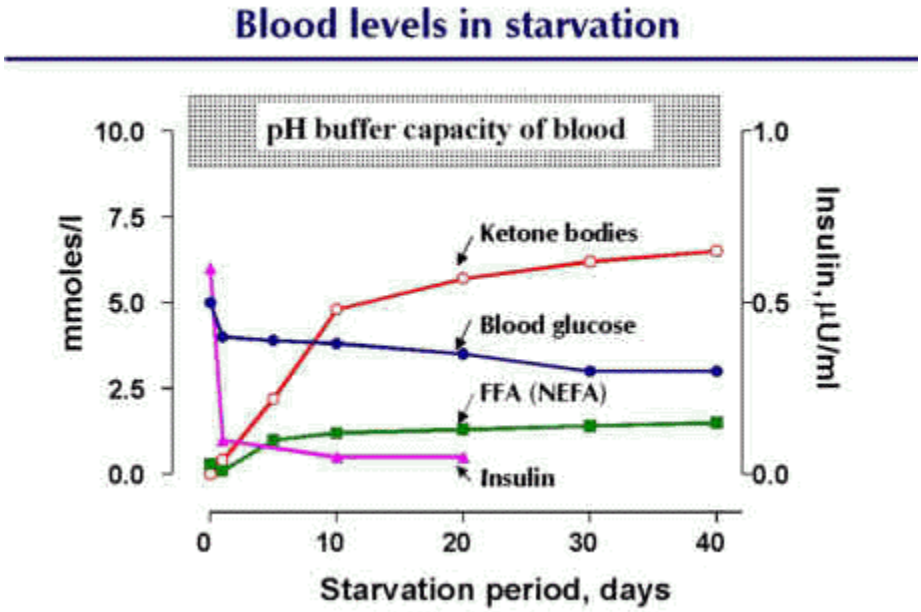
We have data about the total extent of the oxygen supplied to the human liver. Calculations based on this (and assuming that all of this oxygen goes to support conversion of amino acids to glucose) suggest that the maximum capacity of hepatic glucose synthesis from amino acids lies around 400 grams/day. This is the equivalent of approximately 1600 kcal, close to the basal metabolism of a bed-ridden person and hardly enough to support an active life.

Now we can explain "rabbit starvation" and the weight-reducing effects of low-carbohydrate high protein diets. Proteins and the amino acids derived from these are "burned" as glucose. Conversion to glucose is mandatory if the energy in these is to be utilized. Consumption of more protein than can be converted to glucose simply results in loss of these as amino acids in urine.

If the carbohydrate content of the diet is low, amino acids can and do supply the glucose necessary to hold a stable blood sugar level and brain activity. In starvation, the body uses its own proteins. With a high protein diet these come from food.

Circulating Nutrients in Starvation.

The blood glucose level seen in starvation is somewhat lower than in the fed or fasting individual, lying around 3.5 mmol/l. Now, the observant student will say, "what about the brain? How does the central nervous system get enough energy at that low glucose concentration?" The answer is that the same set of hormones that turn on gluconeogenesis and inhibit protein synthesis also increase lipolysis, increase circulating fatty acids and promote ketogenesis. We can see from the figure that the levels of these fuels increase parallel to the decrease in blood glucose. After about 2 weeks of adaptation, about 50 % of the brain's energy comes from glucose, and the remaining 50% from oxidation of ketone bodies. "Ketone bodies" is a terrible expression in my opinion. Remember, they are neither "bodies" or particles and are



organic acids (acetoacetate and ß-hydroxybutyrate). As long as their concentration is under about 9-10 mmol/l everything is OK. If they increase over this level they exceed the blood's capacity to neutralize acids, the blood pH falls and we have develop ketoacidosis. Diabetic coma follows, leading to death if not treated.

Note that insulin levels in starvation are low but NOT absent. The balance between insulin and the stress hormones holds blood sugar, fatty acids and ketone bodies at levels that support life for 40 or more days of starvation. Without insulin or response to insulin, ketoacidosis soon takes over.