Amy Yasko on CBS C699T

Hopefully this will help to clarify what I see as the CBS C699T relationship between ammonia, BH4 and the urea cycle. Also I have heard that there has been a lot of talk about ammonia on this site lately. Perhaps this will help to get parents up to date on where I am in understanding this process.

If an individual has the CBS up regulation (C699T), then they will break down homocysteine more rapidly. This depletes intermediates in the methionine cycle as well as making more products from homocysteine. Homocysteine will be converted to cystathionine. This in turn goes to produce cysteine plus alpha keto glutarate and AMMONIA. What happens next depends in part on the level of cysteine. When there are higher doses of cysteine the body will then convert these intermediates to taurine. (Taurine can be broken down into AMMONIA by bacteria in the gut.) However if there are lower amounts of cysteine the body will choose to make glutathione. So, first of all, the amount of cysteine will help to determine whether we make glutathione or taurine. (J. Nutr. 133:2697-2702, September 2003). If we have the CBS C699T we will be creating higher levels of cysteine (due to enhanced breakdown of homocysteine) so we will almost always be generating taurine rather than glutathione. While the temptation may be to add glutathione (due to low glutathione levels), this can create problems. High levels of certain sulfur byproducts can cause problems in the body. The CBS up regulation is generating so many sulfur products that added glutathione may be a problem for these individuals. So a sensitivity to sulfur products and sulfur containing antibiotics may also be indicative of this mutation. Molybdenum is used to help to convert the neurotoxic sulfite to sulfate. This reaction will be heavily taxed in individuals with CBS C69T + + and so you will often see low levels of molybdenum in spite of constant supplementation. So individuals with a homozygous CBS C699T will often have no homocysteine, high levels of taurine (without supplementation) and low levels of glutathione on a urine amino acid test, as well as low levels of molybdenum on an essential element urine test.

What may more be of greater importance is that when the need is for energy, and not for cysteine, homocysteine produced is metabolized by homocysteine desulfhydrase to alpha KG, NH_3 and H_2S. (see series of articles by Stipanuk, MH). Because we are dealing with mitochondrial issues in most cases we are energy depleted. Methylation cycle mutations will compound this energy problem as SAMe is used as a methyl donor for carnitine and COQ 10, both important energy components of mitochondria. Due to the enhanced conversion of homocysteine we are constantly depleting intermediates of the methylation cycle. This includes SAMe (needed in this case for carnitine and COQ10) as well as methionine. Both methionine and SAMe are also useful for dealing with ammonia, however due to the CBS C699T we are generating more ammonia and less methionine and SAME. The more we supplement (which we need to do) the more ammonia we generate, a true catch 22.

So AMMONIA is generated as a result of transulfuration when cystathionine is converted to cysteine, from taurine as well as from alpha KG. Under ideal conditions ammonia will be absorbed in reactions between glutamine, glutamate and alpha KG. However, (see slides 113 to 116 from MTHFr, Metals and Methylation ppt) aluminum interferes with glutamate dehydrogenase and mercury interferes with glutamine synthase. This impairs the pathways that are normally used for addressing ammonia. In addition, in some individuals the GAD enzyme may be impaired as a result of viral infection and methylation status (discussed in the autism book and in the Boston DVDs). This will create a possible scenario where excess alpha keto glutarate is being generated by breakdown of homocysteine but it cannot convert properly to form i.e. GABA. However this excess alpha KG can combine with the excess ammonia to form more glutamate. I have previously discussed at length the relationship between glutamate, excitotoxins and nerve damage.

The ammonia problem can worsen with viral infection. So for an individual with the homozygous CBS it is a real catch 22. We need the SAMe and methionine (and Folapro and Intrinsic B12 for that matter) in order to have methylation so that we can silence the virus and reduce the viral load. However, every time we add anything that helps the cycle to flow properly we end up generating more homocysteine, which flows directly to make more ammonia and sulfur groups, and taurine. We need to address this part of the cycle in order to get out of the catch 22 we are in. We are currently evaluating RNAs that may be helpful to support healthy ammonia levels.

Ammonia will be converted to urea via the urea cycle. This is an expensive process from the standpoint of BH4 as it uses two molecules of BH4. So the conversion of elevated levels of ammonia can quickly drain limited stores of BH4. This can then impact the levels of serotonin and dopamine. I believe that this is part of the reason why the combination of a CBS C699T + + with the A1298C homozygous mutation (which I believe impacts the reverse reaction through the MTHFR to generate BH4) can have such a devastating effect.

You are correct that arginine is a starting point in the urea cycle. However, I do not believe that arginine is the rate limiting factor here. I think that BH4 is the rate limiting factor in most cases. Arginine can stimulate the growth of virus. This has been particularly well studied for herpes virus. So adding additional arginine may lead to increased growth of herpes virus and may not help the urea cycle if it is not the rate limiting factor.

Arginine that is not used by the urea cycle can be used to make creatinine. So if we can decrease the amount of ammonia that is generated. Then we are using less BH4 and less arginine in the urea cycle. This will free up BH4 for serotonin and dopamine. It will also free up arginine for creatinine.

This is all lovely in theory, but what do we actually see in practice? When we go to a low protein diet, we observe an increase in creatinine and

an increase in metal excretion. This would suggest that we may be on the right track in addressing this problem. This is another reason to monitor urines carefully as it may appear as if behaviors are deteriorating and that a low protein diet is not working, when in fact this is a result of increased creatinine and metal excretion. I suspect that some of the behaviors that have been attributed to yeast (silly behavior following food) may in fact be high ammonia levels generated as a result of CBS up regulation. This imbalance in ammonia levels will most likely contribute to gut imbalances and exacerbate yeast issues.

I have also been spending a lot of time looking at Reye's syndrome. This occurs following a viral infection and the use of aspirin or other salicylates. It appears that the salicylates have an effect on mitochondrial energy production.(another tie in between energy, mitochondria, virus and metals) In susceptible individuals this effect on the mitochondria leads to ammonia buildup and a drop in blood sugar levels. Children with mutations in the urea cycle will have the greatest issue with Reye's syndrome. Some of these elements should sound familiar...virus, sensitivity to salicylates, high ammonia, blood sugar issues. So I am looking in to this area to see if there are some answers for us here. The use of carnitine and ATP to aid in energy production should be beneficial. Recently I have been contacted by a number of parents of children with Mitochondrial Disease. I think that this is related to CFS, FM and many of the factors discussed here relate directly to Mitochondrial Disease.

The good news is that the more we understand what is going on the easier it is to address it. We are in the process of evaluating the benefits of low protein diets, RNAs and the possible use of BH4 supplementation to address these mutations. Each day we move a little bit closer to getting the necessary answers to know how to address these issues.