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SUBJECT: GABA & GLUTAMATE – Part 1

Fellow Fibbers,

This post will start with VMAF and end with AMAF.

Vagal tone is determined primarily via the neurotransmitter glutamate (GLU). Please review my BB post of 3/9 for details and references on the autonomic nervous system (ANS) and VMAF. As demonstrated in that post GLU is integral in mediating the increase in respiratory sinus arrhythmia seen in the physically fit. VMAF is top heavy with such individuals. Many of you know me to be a strong proponent of Mg supplementation. So, what is the connection between GLU and Mg?

There have been several recent posts that provide some telltale clues.

In a post on the BB Jackie on 3/17/03 introduced us to the term “Biochemical Individuality.” (1) “People have genetically determined and highly individualized nutritional requirements." (2)

(1) Biochemical Individuality, Roger Williams, NY Wiley and Sons 1956, New Caanan, Conn. Keats Publishing, 1998
(2) The Metabolic Typing Diet, William Wolcott, Doubleday 2000, ISBN 0-7679-0564-4 (p. 25)

Fran in a post on 3/15 in the Conference Room stated:

Eliminating as much glutamate, or at least free glutamate as possible is what stopped my AF. I have not had AF since. However, what it left me with was PRH (postprandial reactive hypoglycemia), which will give me ectopics, but will not lead to AF. Maybe I had PRH all the time, but the effects only became noticeable after elimination of free glutamate. So while glutamate is touted as a great supplement and essential to the body, I believe that afibbers have too much, and do not manufacture GABA in sufficient quantities - and hence AF.

And then on 3/16 she posted:

To be quite honest I think glutamate toxicity underlies every known trigger, symptom, hypoglycemia, deficiency of mineral and excess intracellular sodium and calcium etc relevant in AF.

And then on 3/11:

It may be a substrate of VMAFers that they are thin, with fast metabolism, prone to PRH with high insulin levels, low body temp, low blood pressure etc - to me the opposite of diabetes.

I find the posts of these two exceedingly perceptive contributors to this BB most insightful and motivating. But I have to thank Erling for truly opening my eyes to the connection between nutrition and VMAF. In this post I hope to convince you of exactly how Mg and GLU are connected, at least in VMAF and to a certain extent in AMAF as well. This connection leads to a very easily designed supplemental regimen that might possibly eliminate VMAF. I have followed this regimen for the past week or so and have experienced a complete and sustained frame shift in my HR and HRV, higher and lower respectively, for the same activity at the same time of day. I still get PACs and many dropped beats, especially at night, but the low vagal tone seems to protect against an episode.

<u>The Facts</u>

1. GLU is the most important excitatory neurotransmitter and GABA is the most important inhibitory neurotransmitter in the CNS. Glutamate decarboxylase (GAD) controls the rate-limiting step in breaking down GLU and creating GABA. In addition, it is pivotal in the synthesis of the neurotransmitters serotonin and dopamine.
2. Vitamin B6 is a required coenzyme for this decarboxylase (apoenzyme+coenzyme=holoenzyme). Two enzymatic steps are required for the conversion of inactive Vit B6 (pyridoxine) to active pyridoxal-5-phosphate (P5P or PLP). The first is phosphorylation of pyridoxine by pyridoxine kinase, which itself requires magnesium and P5P. The second is oxidation of pyridoxine phosphate, which requires riboflavin (Vit B2). This active P5P then combines with Mg (or Zn) to serve as a cofactor with glutamate decarboxylase.
3. Vitamin B6 deficiency is the most common Vitamin B deficiency. The B vitamins are all water-soluble.
4. “An alternate form of a gene present in > 1% of the population is called a polymorphism. Some polymorphisms that are associated with a phenotype have been shown to alter cofactor binding and affect a large percentage of the population” (1). Phenotype refers to a measurable difference in expression of different genes (genotype). Different genotype does not necessarily mean different phenotype. This is the essence of “biochemical individuality”.
5. Polymorphisms of Vitamin B6 are probably the most common (1).
6. As of 2002, of the 3870 enzymes catalogued in the ENZYME database, 860 (22%) use a cofactor. P5P is utilized by 112 (3%) of these 3870 enzymes (1). Mg is a required cofactor for nearly 350 different enzymes (112 of these involve P5P).
7. It is estimated that about 33% of U.S. households are deficient in vitamin B6, which must be replenished regularly (2). Vitamin B6 deficiency can lead to impaired neural functioning that can sometimes be reversed, but only after months or years (3). According to the National Academy of Sciences 80% of Americans are Mg deficient (4).
8. GAD would be the very first enzyme to feel this shortfall, since this decarboxylase has less affinity for P5P than any other. This is in the absence of any associated polymorphism (5).
9. P5P is a coenzyme in the metabolism of amino acids (including the synthesis of taurine), fats (including sphingomyelin and phospholipids) and in the breakdown of glycogen.
10. B6 deficiencies impair conversion of alpha-linolenic acid to EPA and DHA, with the most pronounced reduction in production of DHA (6).
11. B-6 requirement increases with age.
12. Orthomolecular medicine, a term coined by Dr. Linus Pauling, treats relative vitamin dependency. Orthomolecular psychiatry is a branch of orthomolecular medicine andd was pioneered 30 years ago in Saskatchewan by two Canadian physicians, Doctors

Abram Hoffer and Humphey Osmond. You may recognize that first name as one of Hans' associates in Victoria. Orthomolecular medicine is at the heart of polymorphism.

13. Animal studies suggest that the excitatory function of glutamate plays a key role in controlling gastric function, with high glutamate causing a depression of gastric motility (7).
14. Since alpha-ketoglutarate and B6 are cofactors in this GABA metabolic pathway, they can be used to alleviate this metabolic impairment (8).
15. GAD is present in high levels in the hypothalamus and synthesizes GABA from glutamate.
16. GABA may also have therapeutic benefit by reducing the triggering of transient lower esophageal relaxations, which are the major cause of gastroesophageal reflux (GERD) (9).
17. GABA receptors in dorsomedial hypothalamus regulate heart rate, blood pressure and plasma norepinephrine level via inhibition of norepinephrine, serotonin and dopamine neurons (10).
18. There is a significant relationship of dopamine and GABA. In general, GABA acts to reduce the firing of the dopaminergic neurons (11).
19. Hypoglycemia induced catecholamine secretion is counterbalanced by hypothalamic GABA (12).
20. GABA inhibits the dorsal raphe nucleus and increases REM sleep (13).

Hypothesis:

1. VMAF is seen in those with a polymorphism for GAD. This mutation results in less affinity of the enzyme for glutamate.
2. Excessive glutamate causes increased vagal tone. This tone is already increased in those most at risk for VMAF, the physically fit (see post on the BB about RSA and VMAF).
3. The onset of VMAF is determined by the dietary intake and absorption of Vit B6 and Mg, required cofactors for GAD.
4. This vagotonia causes shortening of the atrial refractory period, increased dispersion of refractoriness, slowing of cardiac conduction velocity and only needs a little ectopic automaticity to trigger an episode of AF.
5. However, this is not the only manner in which VMAF can be triggered. GABA in the hypothalamus is required for the proper regulation of blood glucose. In its absence there is hypoglycemia and reactive catecholamine synthesis. Catecholamines are also secreted anytime there is perceived dehydration or hypovolemia (low blood volume). The latter can occur after a hot bath (especially with alcohol), which can cause peripheral vascular dilatation and relative hypovolemia. It can also occur in the postprandial period, when there is congestion of the splanchnic bed for GI absorption and relative hypovolemia. Catecholamines can also cause shortening of the atrial refractory period. They also trigger automaticity.
6. Vagal maneuvers trigger VMAF through excess glutamate. Circulating catecholamines trigger VMAF through insufficient GABA.
7. Insufficient GABA is responsible for the poor sleep pattern of VMAF.
8. Insufficient GABA is responsible for sexual activity triggering VMAF.
9. Insufficient GABA is responsible for GERD triggering VMAF.
10. This can all be overcome by markedly increasing Vit B6 intake. For example, if an enzyme has lost 80% (or 4/5) of its original affinity for a cofactor because of the polymorphism, then by increasing the concentration of that cofactor by a factor of 5 the same end result can be obtained. Please read the recent article at hyperlink #1. It is excellent. As Fran indicated, this is not enough to produce GABA, although I have found that it does a very nice jod of removing glutamate. My HR and HRV have exhibited a frame shift of 10-15 bpm higher and 10-15 ms lower HRV.

11. In order to increase GABA, one must also take alpha ketoglutarate (14) and GABA. The former combines with NH4 to make glutamate and force the reaction back toward GABA through GAD. The latter should provide direct assistance. GABA does not cross the blood brain barrier. However, the hypothalamus and the paraventricular nuclei (including the dorsal raphe nucleus in the pons) have no blood brain barrier.

VMAF and AMAF are not two ends of the same spectrum. They are two different diseases. There is a different age and gender predilection for each. This is not to say that VMAFers cannot trigger an occasional episode that appears to be of sympathetic origin. This is not to say that AMAFers cannot achieve improvement by increasing their Vit B intake. Please read the following excellent article entitled: High-Dose Pyridoxine as an "Anti-Stress" Strategy at http://www.pantox.com/research/Publications/b6.html

For those concerned about toxicity at doses of several hundred mg per day please read the pertinent section at:
http://www.foodstandards.gov.uk/multimedia/pdfs/evmpart2.pdf

Polymorphism is at the forefront of orthomolecular medicine and is one of the hot topics in genomics. For additional information, please read:
http://www.emedicine.com/NEURO/topic680.htm

Additional useful information:

Increased dietary protein and exercise both increase the need for B vitamins. In humans a 100 mg dose of Vit B6 will produce a plasma peak in 2 hours with a subsequent half life of 8 hours. Doses of over 25 mg produce little change in plasma P5P. Observations during clinical treatment of patients who need vitamin B-6 supplementation have shown that when P-5-P is indicated, it is 10 times more effective than pyridoxine HCl. Both GABA and alpha ketoglutarate are commercially available, at least in the US.

Empirically I am completely convinced of the role of GLU in VMAF. I am still experimenting on the GABA end and will keep you informed. GAD gets my vote for the defective substrate in VMAF.

1) http://www.stopping-cancer-naturally.org/pdf/study.pdf
2) http://www-unix.oit.umass.edu/~excs597k/sacco/B6.htm
3) http://facultystaff.vwc.edu/~jeaster/courseinfo/312/312Nature2001.html#Pyridoxal Phosphate
4) http://www.mgwater.com/minimum.shtml
5)http://www.science.com.br/henrys_corner/artigos_tecnicos/novos/effects_of_physical_activity_on_thiamine.pdf
6) http://www.findarticles.com/cf_0/m0FDN/1_6/71948217/p1/article.jhtml?term=carpal-tunnel
7) http://www.metametrix.com/docs/book/ch4.htm
8) http://www.metametrix.com/docs/book/ch4.htm
9) http://oac3.hsc.uth.tmc.edu/apstracts/2001/gastro/June/114g.html
10) http://www.nencki.gov.pl/pdf/an/an6034.pdf
11) http://www.unifr.ch/biochem/DREYER/Neurotransmitters/gaba.htm
12) http://oac3.hsc.uth.tmc.edu/apstracts/2000/regulatory/November/432r.html
13) http://www.bio.brandeis.edu/BANG/bang98session.html
14) http://www.metametrix.com/docs/book/ch4.htm

PC, MD v54

Hello PC,

You've been very busy. This is outstanding research and certainly makes a lot of sense. I haven't finished reading all your links, but will do so tomorrow. I did start taking P5P and it has aKG in it. I don't remember the dosage of aKG, as I threw out the bottles by mistake, but I think it was 50mg of P5P and 25mg of aKG, made by Country Life. I have been keeping track of my HR, blood pressure, and diet everyday, but haven't seen a marked difference in the first two, as of yet. I've only been taking for 3 days. I did forget to take my meds last night and had no problems today, so I'm not taking again tonight, but will continue the morn dose for another week, and then try to eliminate altogether. I'm still continuing my diet of meat, veggies, and salads with occasional cottage cheese. It is strange that the last time I purposefully eliminated my eve. Norpace, I awoke in AF and this time I didn't after taking P5P for three days. Could be just a coincidence, but time will tell. I am still amazed at how strong my heart beat is and how good I feel. There have been some skipped beats on occasion, but the last couple of days, there have been none.

I want to personally thank you for this very important contribution and the time I know you have spent researching. My thanks to Fran and everyone else, as well, for their insights. I believe we are on the road to recovery.

By the way, I contacted Metametrix, and they gave me the name of a doctor in my city, that uses their labs. I have an appt. with Dr. Mary Griffith on 4/10, and I plan on having an amino acid panel done, along with other testings, suggested in the book "Laboratory Evaluations in Molecular Medicine". I really want to know all there is to know about what is going on in my body, so I'll keep you posted, as things progress.

Much respect,

Richard

Richard,

Thank you for your post.

The web link you contributed on aKG (thanks much) contained a section on increasing GABA through aKG. http://www.metametrix.com/docs/book/ch4.htm

The recommended dose was 600 mg bid to increase GABA and tid to decrease glutamate (along with Vit B6 on both counts). So you ought to consider increasing the aKG from 25 mg.

Regarding any change in HR while on P5P, I can detect a distinct change because I use the Polar S810. There has also been a distinct increase in skipped beats, especially at night. These are definitely not PACs and are of no risk for triggering LAF. I've been doing a lot of thinking about them and my theory is that the mechanism is as follows:

1) The firing rate of the SA node is controlled by the right vagus nerve.
2) The left vagus controls the AV node by changing its conduction velocity.
3) The former is intimately involved in determining ones RSA (respiratory sinus arrhythmia).
4) RSA is under the aegis of the NTS (nucleus tractus solitarius) and the NA (nucleus ambiguus) in the medula oblongata. They receive the sensory signals (afferents) and send the motor signals (afferents) respectively.
5) Glutamate is the neurotransmitter for this function.
6) The DMN (dorsal motor nucleus) also controls the vagus nerve efferents and is thought (not proven yet) to control the diurnal change in vagal tone.

The above is all known and well accepted. My theory is that the AV node is primarily under the aegis of the DMN is controlled in some way by GABA (in addition to glutamate). In the absence of GABA there is more diurnal slowing of AV node conduction velocity. Since the P5P leads to less glutamate and a higher HR, this means that any given impulse from the SA node is more likely to encounter a refractory AV node and result in a dropped or skipped beat.

I plan to follow this latter (as well as sleep pattern) very closely during GABA supplementation. If this works then I'm going to try to induce a typical low GABA type AF episode (you know my favorite method for achieving this), but premedicate with GABA. I'll keep you posted, if you keep me posted.

PC, MD v54

P.S. I'm involved in some research on VMAF with Dr. Stephen Porges, the originator of the Polyvagal Theory. VMAF appears to offer some further insights into the functioning of the vagus that may enable expansion of his theory.

Hello PC,

Thanks for the dosage on aKG. The qty. of mg. in the P5P was for each pill and I am taking 3x daily to get 150mg P5P and 75mg of aKG. My other vits have P5P in them, as well, so I am getting approx. 200mg a day. I will up my dose on the aKG, but will have to get some.

I forgot to pass along some interesting info. last night. My wife was speaking to an acquaintance on Sat. and her dad has AF. When he was admitted at Overlake Hospital in Bellevue, WA, with AF, the cardiologist on hand, started rubbing the back of the neck with his thumb, up and down from the base of the cranium, next to the spine, and down the neck. She thought it was on the right side of the neck. By doing this, it brought her dad back into sinus rhythm. I think I would try both sides. The strange thing about this is that someone came into my office several years back, and I happened to have the hiccups. He asked if he could show me a technique for ridding the hiccups, and of course I said yes. He took both thumbs and placed them at the base of the cranium, thumbs pointing to spine, on each side of the spine. He then placed each middle finger on each temple, next to my eyes. He exerted upward pressure with the thumbs, right under the skull base and some pressure with the fingers and held for about 30 secs., and my hiccups were gone. I have used this method on many people and it has always worked. It may take some practice, for the hiccups, as my wife has a hard time trying to do it. Massaging the neck may be just a quick fix for AF, and certainly one needs to change one's diet, but maybe this will work instead of on demand meds. It brought this man back into SR without cardioversion, however he is 90 now, and on meds and warfarin. I certainly know the hiccup technique works, and people have been amazed. The next time I have an AF attack, and hopefully that won't happen, I'll have my wife massage my neck and see what happens. I'll let you know.
Just think, PC! AF trigger at night and massage in the morning. Maybe this isn't such a bad thing. I'll post this on the BB, to make sure everyone sees, as well, and maybe everyone can at least try and see what happens. The worst case is a good massage from a loved, and that can't be all bad.

Richard

Richard,

Most interesting. I'll try it, if and when.

Don't forget your Mg supplements. It is also most important. I'm beginning to think that Zn is also important and easily overlooked.

GAD is unique in many ways. It is the most likely culprit because:

1) It involves a neurotransmitter substance on either end of the reaction. Any shortfall in enzymatic activity is a double whammy - too much of one and not enough of the other.
2) It is one of the few enzymes that require not only a coenzyme (P5P=PLP) but also a mineral cofactor (Mg or Zn). This enhances the likelihood that some mutation (incorrect single amino acid substitution from a long ago progenitor) in the enzyme might result in loss of or decreased affinity.
3) P5P is required (by pyridoxal kinase) to create P5Pand Mg is required (by ATP) for absorption of Mg. Not one but two catch 22 situations.
4) The typical Western diet is terribly deficient in both B6 and Mg.

PC, MD v54

PC,

Wow! Many thanks for your knowledge and impressive efforts in tracking down "the beast". I look forward to soon seeing your work published in a formal journal, to be taken advantage of by all afib doctors and their patients.

Your post makes me want to add to my personal afib story. I have always said that the elimination of my afib, which I now understand must have been "vagally mediated", was accomplished by three things: optimizing intracellular Mg; optimizing mitochondrial energy (ATP) production; and optimizing cell membrane structure and function by optimizing dietary fats. I never mentioned that I was also taking fairly high dose vitamins B6 and B2, because I didn't understand their possible role in the etiology of my afib until now. My story:

When I was 40-something a fall on a construction job tore muscles and ligaments in my right shoulder. In time where was sufficient healing to allow mostly full use of my arm, even though the shoulder would dislocate easily. Many years later it became quite troublesome because of aching pain, especially in the evening and at night, although I had long since substituted a desk for scaffolding. It became such a problem that I considered surgery, but I was told by the top shoulder surgeon in Denver, Dr. Donald Ferlic, that although repairing the muscle and ligaments could certainly be done, it would not guarantee elimination of the pain, so I procrastinated.

I had also developed a pretty poor blood lipid profile, high cholesterol, etc., and learned that high dose B6 could be helpful -- this from Dr. Alan Gaby (between Mg and B6 I owe him a lot). One evening, several months after starting with B6, 100 mg per day, still struggling with the surgery decision, I suddenly realized to my astonishment that my shoulder wasn't aching -- by the way, this was several years before afib began. Thinking there was probably a connection with the B6 (I wasn't taking any other supplements), I read up on B6 involvement in nerve myelin sheath integrity and tissue healing in general -- there is a lot of information regarding curing "carpal tunnel syndrome" with high dose B6 and B2: "Vitamin B6 in doses of 100 to 200 mg per day may, in the future, may be the drug of choice in the treatment of CTS." (George S. Phelan, the orthopedic doctor who pioneered surgical treatment for CTS in 1947, writing in The Journal of Hand Surgery in 1981.) Further on I read about B6 and B2 being the most important cofactors in amino acid metabolism: "Pyridoxine, or vitamin B6, is the most important vitamin for amino acid metabolism because it is the cofactor for the important enzymes called transaminases, which metabolize amino acids. Riboflavin (B2) and niacin (B3) are the next most important... In some ways the B vitamins are amino acids, but they are not incorporated into proteins." (The Healing Nutrients Within. Eric Braverman, MD, and Carl Pfeiffer, MD, PhD.) "Most forms of pyridoxine are inactive. In order to be converted to the active form, they need B2." (Karl Folkers, PhD, a key

figure in elucidating the structure of B6 and its synthesis. In the late 1950's he and his co-workers were the first to identify the structure of and to synthesize coenzyme Q10.)

I have never discontinued taking multi B vitamin tablets, 50 to 100 mg of B6 and B2 daily, plus the full spectrum of other B vitamins. When afib kicked in I ultimately added Mg, CoQ10 and carnitine, EPA and DHA oils, and after many years the afib went away (although not until I added the fish oils and eliminated bad fats). Now, thanks to your dogged efforts, I can understand how and why B6 and B2 were probably also part of the cure.

Many, many good people have my gratitude -- Karl Folkers for his pioneering research on B6 and CoQ10; Alan Gaby for enlightening me on B6 and Mg; Carl Pfeiffer and Eric Braverman for their research, specifically on amino acids, their functions and effects; Jackie and Fran for their insights and determined sharing of their knowledge and experience; also the many other contributors to these forums for sharing their insight, personal experiences, and thought provoking questions; Hans Larsen for his knowledge and for making all of this communication possible; and you, PC, for continuing to pull it all together. Thank you all very much! Here's hoping that your efforts will soon free all of you from this nasty affliction!

Erling, 74 ex.

The following preliminary results from LAFS V may be of interest in the GABA/glutamate connection:

Prevalence of diabetes

Adrenergic - 0 out of 24 (0%)
Mixed - 1 out of 57 (1.8%)
Vagal - 0 out of 96 (0%)
All paroxysmal - 1 out 0f 177 (0.6%)

Prevalence of Impaired Glucose Tolerance

Adrenergic - 0 out 0f 18 (0%)
Mixed - 1 out of 52 (1.9%)
Vagal - 2 out of 75 (2.7%)
All paroxysmal - 3 out of 145 (2.0%)

Prevalence of Hypoglycemia

Adrenergic - 10 out of 24 (41.7%)
Mixed - 14 out of 57 (24.6%)
Vagal - 20 out of 83 (24.1%)
All paroxysmal - 44 out of 164 (26.8%)

The overall prevalence of diabetes of 0.6% is clearly significantly lower than the 3-9% rate found in the general population. I believe this is an important clue.

Hans

Hans,

The greater incidence of hypoglycemia in AMAFers (v. VMAFers) is even more striking since it

would seem that catecholamines would be higher in AMAFers. This should cause hyperglycemia and not hypoglycemia.

PC

Erling,

Thanks so much for the history lesson. Your long hours of investigation are clearly apparent in your familiarity in such matters. It is impossible to even attempt to connect dots that don't exist. Your mention and recognition of the stalwarts that discovered them is much appreciated.

I'm sure I'm not alone in saying how much I enjoy reading the personal story of one who has surmounted "the beast".

I don't for a moment doubt that there are many GAD polymorphisms that can eventuate in LAF or that there are other enzymes that can be involved.

Although I am very optimistic about being on the right track, I have had so many misfires to date. We'll see what GABA does.

PC

It's a Nobel Prize for you PC. You have to get this published. I am so glad that I kept plugging the glutamate link (even though I am sure many got sick and tired of it) and thanks to you PC I am now about to try P5P as I reckon that although I am getting it in diet form my body is not doing what it should with it. I may just add B2 because I can relate to Erling's shoulder problem. I will be back in the city again on Thurs to buy some and experiment.

This is a huge turn around for me as I am so scared of supplementing because of the bad experiences I have had. But won't it be so nice if I could go out and eat a posh meal again .....

Fran

Fran,

You're my idol when it comes to brute determination.

It seems to me that your diet wrt Vit B intake, Mg, etc., and glutamate avoidance is just fine. It's the GABA that you might be slightly short on. I think those PACs you talked about that never trigger LAF are skipped beats and not ectopic beats. I think these skipped beats are due to low GABA. Will let you know how GABA affects my skipped beats.

Perhaps a dinner out is in your future.

PC

PC

To be quite honest I am not sure what my heart is doing now. All I know now is there is no AF.

I've been through the whole gamut of arrhythmias near enough. The last time I had my pulse taken by a Dr (the homeopath) she said I had a couple of early beats but it was steady. Would early beats equate to skipped beats?

Fran

Fran,

I can only speak with authority on my situation because I use a Polar heart monitor and can see the recording (skipped beats show the bpm to drop to exactly one half the going HR). With this biofeedback I can tell the difference between a PAC and a dropped beat quite easily. The interval is twice as long and there is no "palpitation", or increase in strength of the next beat. Beats are the same with an occasional prolonged interval. My PACs are still present but their frequency has dropped from a couple per minute to one every 10 or 15 minutes.

My question was predicated on a statement that you had made earlier indicating that you continued to have increased PACs but that these never eventuated in LAF. If these were truly PACs, then I would be surprised that they hadn't triggered LAF.

PC

PC

I hope you get your long awaited good sleep. For me lack of sleep was the worst thing as it just amplified everything tenfold. For a one off had you considered taking a valium? Seemingly valium fits the GABA receptor and does the same job. Of course none of us want to end up on valium, but it could indicate whether GABA is the problem. Mind you, the hangover in the morning it will leave may not be worth that nights sleep.

Interesting what you were saying about ALS. I had at one point in the height of my AF and other things suspected a form of sclerosis as I would get numb patches, burning patches, my legs would buckle, I would drop a cup out of my hand when thinking I was holding it, at worst I would get disorientated and walk into walls and I would choke on food (it happened a few times when out and it was really frightening and had to be saved a couple of times with thumps and once the Heimlich manoeuvre) etc. But it was all transient and never continued for any length of time. I told my Dr and he said it happened to everyone from time to time and I was over reacting. He thought I had depression and I said it was anxiety. So I just said well all I know is my body is not doing what it should, it is not reacting properly. This started happening after 18 years of AF, so I suspect you are not far off the mark when you say that some of us with LAF may be on the road to ALS. And for me keeping low glutamate levels does the trick. Perhaps it is not such a high price to pay.

I haven't had runs of PACs and PVC's for a while now. But yes, I was plagued by them. These definitely were ectopics as they were recorded on ECG and holter monitor after my AF had stopped months beforehand by eliminating free glutamate. For whatever reason they did not turn to AF, I can only surmise through a lack of excitory free glutamate. This may, however, have turned the activity to the sinus node as you indicated in one of the above posts. IT will all fall into place soon though.

The high protein diet has put a stop to these runs of ectopics. But as I said the homeopath said I had a couple of early beats. I stupidly never asked what she meant by early beats. Don't know if they mean ectopics or not.

Thanks again for your diligence on this very important matter. I am glad you are working with someone else on it. Can I read about Dr. Stephen Porges work on the Internet?

I'm off to do a search anyway,

Fran

Fran,

Try the following for a taste of Porges:
hyperlink http://www.wam.umd.edu/~sporges/polyvag/polyvag1.htm

This is his seminal work on the polyvagal theory. It's not too technical, but it's definitely not light reading either. It's not directly applicable to VMAF, but does demonstrate where the forefront of what is known about RSA and the vagus lies. The RSA connection caught my eye.

I must say that working toward improvement is much easier when someone has shown that the path exists.

I just ordered some arginine and ornithine supplements and will experiment with them if I get nowhere with the GABA. Thanks for the suggestion on Valium. I'll just write myself a prescription.

PC

Fran,

Sick and tired of your plugging the glutamate link?? I found the back-and -forth between you and PC absolutely fascinating and hugely informative. I have to say that your insights and researched information are beyond interesting! This might well turn out to be the missing link. Thank you so much!

Erling

Hi PC,

Well, here again, I'm like Mike (F.that is).

Thanks much for what you are doing. Even though I'm not posting here-I'm reading. In the recent past I was taking 100mg B6 and 500mg GABA nightly with no effect. However, at that time I do not believe I was absorbing Mg very well. I am now taking 500mg chelated Mg and 360mg Magnesium glycinate along with the WW. Before doing the IVs of Mg, I couldn't even take 250mg of the chelated Mg without running to the loo. Not so now. I'm going to add back 200mg B6 and 500-1000mg GABA. I'll report back any happenings.

Thanks again. Much appreciated.

Jim V58

Jim,

You ought to consider switching to pyridoxal phosphate (P5P=PLP) from the inactive Vitamin B6

(pyridoxine hydrochloride) for better coverage of your possible increased B6 needs. And take it in divided doses, e.g., 50 mg q6h. I take 100 mg at the start of a workout to cover myself for the post workout vagal rebound.

I'm still experimenting with how to time the doses. I don't think there's a problem taking P5P with a Mg supplement, but I'm not sure. There seem to be conflicting opinions on this.

Like you I take my Mg in multiple different forms (Mg glycinate, Mg aspartate and ww, as well as a multimineral with Mg malate, citrate, lysinate, tartrate, lactate and orotate.

PC

Hello PC,

I was doing some reading on GAD and am trying to figure out what testings I want done by the new naturopath that uses metametrix. Have you or anyone else had hormone levels checked. This link states that estrogen regulates GAD. Not a long article, but I was just curious.

http://www.med.cornell.edu/mdphd/fac/weiland.html

Thanks for your input.

Richard

Once again, just gotta say:

MANY MANY thanks to all: PC, Fran, Erling, Jackie and (of late) Richard for all of your efforts. (And to Hans - almost goes without saying (-:)

I am for sure going to give the P5P a try. Fran, have you managed to source a P5P supplement in the UK? Please let me know how you get on in this regard.- .. a first look on the web didn't get me anywhere. Also Fran, can one get P5P via foodstuffs and if so which?

I've largely moved out of my 'raft' of supplements lately since I feel I've probably (as I'm oft prone to do) gone somewhat overboard in that regard during the last 6 months, and I like and favour Fran's opinions re getting what we need via diet so far as is poss. My current supplement regimen includes 400mg mag glycinate, 50mg zinc, and 1200mg lecithin per day, and I've just added a Solgar V2000 multi-vit to get inter alia some B vits. (I eat oily fish and kiwis every day without fail - also little or no carbs and all organic.) I would also like to add (in addition to P5P) some akg but cannot get anywhere as regards sourcing some in the UK..... again Fran, any ideas in this regard??

Thanks again guys and gals,
Mike F.

Re P5P in the UK: just answered one of my own Qs..... P5P can be had in the UK in the form of Solgar 50mg tablets.

Mike F.

Mike

Thanks for the Solgar link. Like you I did a search but got confused with all the different plugins. So I decided I was going to ask in the wee whole foods shop I get my extra curricular tit bits from as they do a range of good quality supplement too, and seem to know what they are talking about. I have heard them in action and they are not just making sales. They come right out with it if there is an interaction to be had and recommend something else, but don't push. I like sales pitch like this. Of course their customers come back.

I'm not sure about food sources of P5P, but suspect liver and other organ meats might be the best bet - certainly is for B6. Trouble is I have to force feed myself this. But do it once a week.

PC

I'm not sure with myself about trying GABA straight. MSG sensitive people, for some reason do not do well on GABA for whatever reason. I don't know. Also, many moons ago now I had a discourse with Erling about Hypoglycemia (when I first discovered it and learned it ran in my family). The one thing that I discovered over this discourse was that all my families 'illnesses' or should I say syndromes could be linked to a lack of one of the B vitamins. I never did isolate which one. I tried a vit B complex for a few days and ended up in a terrible state of anxiety. Then I tried brewers yeast. Another disaster. 3rd time lucky. If it is a genetic vit B6 problem, eg can't phopholise it efficiently, then perhaps this will do the trick and help me make GABA direct. I know I get enough balance to make it, so my body is not doing something, and this seems the most likely for me.

Will also let you know how I get on.

Fran

Fran,

Thanks for the heads up. I'll just get my toes wet and not dive in head first with the GABA. But I could sure use a good nights sleep.

I think there are many unrecognized polymorphisms of B vitamin cofactor requiring enzymes. There are 113 different enzymes requiring P5P alone. VMAF is probably only one such manifestation of a polymorphism in GAD.

Not only has modern medicine completely overlooked specific nutritional deficits in the pathogenesis of specific diseases (at least in the last half of the 20th century) but also it has continued to force square pegs into round holes. Biochemical individuality and orthomolecular medicine will undermine the idea of "the normal range" as we know it. Instead of lab tests being a barrier to discovery it will start to assist it.

I'm still investigating on how one might measure the Km or its equivalent for GAD in any individual without requiring an invasive procedure to obtain the specimen. It is suposedly only present in brain, pancreas, testis, ovary and oviduct, not exactly easily accessible organs.

PC

PC Sussed it. Early beats are PVCs. So I must still be having some premature ventricular contractions. Premature ventricular complexes (PVCs). An electrical signal from the ventricles causes an early heart beat that generally goes unnoticed. The heart then seems to pause until

the next beat of the ventricle occurs in a regular fashion.

I'm not worried about them. It's almost as if my AF has gone into reverse and I am going through everything backwards that led up to AF and the saga that dominated my life 20 years. Hopefully they will go away when I get the diet spot on. I'm not as aware of them anymore. Also read up on the polyvagal theory. Brilliant. I know this will go someplace and help a lot of people.

Fran

Richard,

Can't provide anything informative on what to test for hormone wise.

Mike,

I've screwed up a bit. It appears that aKG may not be as helpful as I'd thought. That previously posted info was taken from http://www.metametrix.com/docs/book/ch4.htm

At the very top in Table 4-1 it suggests that if GLU is high then Niacin (Vit B3) 50 mg and Vit B6 100 mg bid if GABA is low - no recs; if GABA is high then aKG 600 mg bid and Vit B6 50 mg.

About halfway down it states:

Glutamic acid is elevated in amyotrophic lateral sclerosis patients due to lowered catalytic rates of glutamate dehydrogenase (GD). Treatment with BCAAs showed a significant benefit due to the stimulation of GD.

ed. - There seems to be a lot of ALS cropping up out there (Tom Watson's ex caddy and another pro golfer to name a few). There are probably more than a few VMAFers (and future ALSers) with a polymorphism of GD (instead of GAD - glutamate decarboxylase).

followed by the statement:

GABA is an important inhibitory neurotransmitter in the CNS. The concentration in plasma reflects CNS levels, and low levels in plasma is characteristic of one subset of patients with depression [41]. The neurodegenerative condition, Huntington's disease, manifests as lowered levels of GABA as neuron loss proceeds. The synthesis of GABA in muscle tissues from glutamic acid and ornithine is the most likely source of plasma GABA.

and finally:

Increases of GABA in brain, ornithine and proline in liver, and serine, glycine, and alanine in all tissues were found when aspartic acid was given along with arginine.

So, Mike, don't order or take that aKG. Sorry about that. However, it appears that increasing ornithine intake and ?branched chained amino acids (BCAA) might help increase GABA. BCAAs - isoleucine, leucine, and valine - are essential amino acids that must be obtained from food because they are not synthesized in man. Plasma levels are low in those with low dietary protein. The amino acids aspartic acid and arginine (also stimulates secretion of GH) further increase GABA.

This is probably why Hans found in his survey that one of the differences between LAFers and ex-LAFers was higher dietary protein in the latter. This was in addition to higher levels of hydration, lower dietary Na/K ratio, lower dietary Ca/Mg ratio, and a few other differences that I

can't recall at this time.

PC

PC,

I was taking P5P 100mg(Pure Encapsulations 50mg/cap) along with 500mg GABA @ bedtime for about three months. Quit because no results. Now maybe because of better Mg absorption will start back and see.

What are possible problems of taking Mg with P5P?

Jim

Jim,

Erling has characterized LAF as a "beast". We all know it to be quite complex. Hence it's solution must also be quite complex, i.e., one solution, however intricate and effective, will probably not work for all.

Your variant appears to be particularly refractory. However, I would encourage you to give it the full court press, even if ultimately unsuccessful.

1) Take larger doses of all the B vitamins (you never know where your defective substrate might be).
2) Take Hans advice and always crush your pills (or else you might end up like Mike with undigested supplements).
3) Take your B vitamins with a protein meal. They are better absorbed in a more acidic milieu.
4) Don't compromise all this by taking them with a competing substance, e.g., Mg with fiber or milk.
5) Don't lower your guard and forget Mg, Zn, hydration, ...

Although it would seem to me that manufacturers (even though in an unregulated industry) would not combine Ca with Mg or with P in a supplement if this compromised their absorption. However, Ca and Mg do compete for the same receptor sites in the small bowel. Why would the P in P5P (P5P may not be absorbed intact) be any less likely to bind Mg than the P in Coke?

If you find the answers to these concerns please let me know.

PC

Hi all,

I want GABA, and note from my Internet trawl of the last few minutes that I can get either Solgar - 50 x 500mg = 25g GABA for £12-ish, or 100gms of GABA in powder from (pure) for around £8-ish..... Am I missing something here or is it just massively more economic to buy the latter?? The powder marketing recommends taking 5 GRAMS of GABA at bed-time..... TEN times the dose in one Solgar tablet! Any comments would be most welcome.

Mike F.

I would suspect the powder is cheaper because you are not paying for packaging and marketing. If the powder is genuinely pure and has nothing added to stop it caking etc, then I would feel better taking that than the tablet from Solgar which has binding agents and fillers etc in it. Even though they are supposedly hypoallergenic.

Just my thoughts

Fran

PC,

Thanks very much for the additional and helpful input. My P5P arrived this morning: 50mg tabs of which I'll take 2 per day with protein. As regards ornithine and arginine: given that I eat high quality protein 3 times per day I feel that I am probably not going short of these substances?? I plan to start increasing organ meats in my diet to at least 3 times per week.

(BTW glad to hear that your PACs are down from every minute to a few per hour. I still tend to get PACs varying from 10 per day on a good day to one every few minutes (with bad patches of a few per minute for a minute or two) for a few hours on a bad day. As regards last weeks range of additional palps for eg, one run of 6 fast regular beats (run of ectopics?), one noticeably long pause - could be likened to breathing out fully and then instead of breathing in again, having to breathe out a bit more and wait a little bit longer than comfortable before breathing in again (wonder if it was an ectopic followed by a dropped/missed beat), and, finally, after 20 weeks (and counting - fingers crossed!) of no a-fib, on Sunday morning I had a very a-fibby feeling palpitation which I thought was a for-sure episode: just as I was about to phone my girl to say I'd be late picking her up/to come over and sit with me, I noticed that all was well again. I guess the palp lasted about 6-8 seconds - kinda think it could have been a short blast of a-fib..... it sure felt like it. If it was, then thinking about it against the background of my more recent and diagnosed a-fib experience, I've probably for the last seven or eight years had quite a few such episodes which were always just put down by my doc (never caught on Holter) as palps/runs of ectopics. If my own a-fib can be once more returned to occasioned bouts of less than a minute (the first such palp I can remember for sure being in 95), then I'll regard that as satisfactory progress (-: Maybe - though I'm knocking on wood saying it - I got my three episodes 'proper' (hrs duration) between Oct 99 and Nov 02 when my system had got fully out of sorts: hopefully the cessation of excessive and binge drinking, adherence to a high protein and v. low carb diet, and appropriate supplementation will slowly help my body (and yours and those others of us here on this forum) to get things back into something approaching decent and more normally functioning shape!)

Mike F.

Mike,

Be careful with the Zn. I'm not that familiar with it, but do know that it's not like Mg or K in that anyone with reasonable renal function can easily regulate wide swings in plasma levels. 50 mg seems like a pretty healthy daily intake (RDA is 15 - not that I give RDAs great credence). Zn competes with Copper and Cu deficiency can create another set of problems.

PC

I know this is long but please read it. It does not seem to be covered by copyright so I have reproduced it in full here. It is basically about free glutamate and what it does to a body.

Not Just Another Scare: Toxin Additives in Your Food and Drink

http://www.dorway.com/blayart1.txt

by Russell L. Blaylock, M.D.

There are a growing number of clinicians and basic scientists who are convinced that excitotoxins play a critical role in the development of several neurological disorders, including migraines, seizures, infections, abnormal neural development, certain endocrine disorders, specific types of obesity, and especially the neurodegenerative diseases; a group of diseases which includes: ALS, Parkinson's disease, Alzheimer's disease, Huntington's disease, and olivopontocerebellar degeneration.

An enormous amount of both clinical and experimental evidence has accumulated over the past decade supporting this basic premise. Yet, the FDA still refuses to recognize the immediate and long term danger to the public caused by the practice of allowing various excitotoxins to be added to the food supply, such as MSG, hydrolyzed vegetable protein, and aspartame. The amount of these neurotoxins added to our food has increased enormously since their first introduction. For example, since 1948 the amount of MSG added to foods has doubled every decade. By 1972 262,000 metric tons were being added to foods. Over 800 million pounds of aspartame have been consumed in various products since it was first approved. Ironically, these food additives have nothing to do with preserving food or protecting its integrity. They are all used to alter the taste of food. MSG, hydrolyzed vegetable protein, and natural flavoring are used to enhance the taste of food so that it taste better. Aspartame is an artificial sweetener.

The public must be made aware that these toxins (excitotoxins) are not present in just a few foods but rather in almost all processed foods. In many cases they are being added in disguised forms, such as natural flavoring, spices, yeast extract, textured protein, soy protein extract, etc. Experimentally, we know that when subtoxic (below toxic levels) of excitotoxins are given to animals, they experience full toxicity. Also, liquid forms of excitotoxins, as occurs in soups, gravies and diet soft drinks are more toxic than that added to solid foods. This is because they are more rapidly absorbed and reach higher blood levels.

So, what is an excitotoxin? These are substances, usually amino acids, that react with specialized receptors in the brain in such a way as to lead to destruction of certain types of brain cells. Glutamate is one of the more commonly known excitotoxins. MSG is the sodium salt of glutamate. This amino acid is a normal neurotransmitter in the brain. In fact, it is the most commonly used neurotransmitter by the brain. Defenders of MSG and aspartame use, usually say: How could a substance that is used normally by the brain cause harm? This is because, glutamate, as a neurotransmitter, is used by the brain only in very, very small concentrations - no more than 8 to 12ug. When the concentration of this transmitter rises above this level the neurons begin to fire abnormally. At higher concentrations, the cells undergo a specialized process of cell death.

The brain has several elaborate mechanisms to prevent accumulation of MSG in the brain. First is the blood-brain barrier, a system that impedes glutamate entry into the area of the brain cells. But, this system was intended to protect the brain against occasional elevation of glutamate of a moderate degree, as would be found with un-processed food consumption. It was not designed to eliminate very high concentrations of glutamate and aspartate consumed daily, several times a day, as we see in modern society. Several experiments have demonstrated that under such conditions, glutamate can by-pass this barrier system and enter the brain in toxic concentrations. In fact, there is some evidence that it may actually be concentrated within the brain with prolonged exposures.

There are also several conditions under which the blood-brain barrier (BBB) is made incompetent. Before birth, the BBB is incompetent and will allow glutamate to enter the brain. It may be that for a considerable period after birth the barrier may also incompletely developed as well. Hypertension, diabetes, head trauma, brain tumors, strokes, certain drugs, Alzheimer's disease, vitamin and mineral deficiencies, severe hypoglycemia, heat stroke, electromagnetic radiation, ionizing radiation, multiple sclerosis, and certain infections can all cause the barrier to fail. In fact, as we age the barrier system becomes more porous, allowing excitotoxins in the blood to enter the brain. So there are numerous instances under which excitotoxin food additives can enter and damage the brain. Finally, recent experiments have shown that glutamate and aspartate (as in aspartame) can open the barrier itself.

Another system used to protect the brain against environmental excitotoxins, is a system within the brain that binds the glutamate molecule (called the glutamate transporter) and transports it to a special storage cell (the astrocyte) within a fraction of a second after it is used as a neurotransmitter. This system can be overwhelmed by high intakes of MSG, aspartame and other food excitotoxins. It is also known that excitotoxins themselves can cause the generation of numerous amounts of free radicals and that during the process of lipid peroxidation (oxidation of membrane fats) a substance is produced called 4-hydroxynonenal. This chemical inhibits the glutamate transporter, thus allowing glutamate to accumulate in the brain.

Excitotoxins destroy neurons partly by stimulating the generation of large numbers of free radicals. Recently, it has been shown that this occurs not only within the brain, but also within other tissues and organs as well (liver and red blood cells). This could, from all available evidence, increase all sorts of degenerative diseases such as arthritis, coronary heart disease, and atherosclerosis as well as induce cancer formation. Certainly, we would not want to do something that would significantly increase free radical production in the body. It is known that all of the neurodegenerative disease, such as Parkinson's disease, Alzheimer's disease, and ALS, are associated with free radical injury of the nervous system.

It should also be appreciated that the effects of excitotoxin food additives generally is not dramatic. Some individuals may be especially sensitive and develop severe symptoms and even sudden death from cardiac irritability, but in most instances the effects are subtle and develop over a long period of time. While MSG and aspartame are probably not causes of the neurodegenerative diseases, such as Alzheimer's dementia, Parkinson's disease, or amyotrophic lateral sclerosis, they may well precipitate these disorders and certainly worsen their effects. It may be that many people with a propensity for developing one of these diseases would never develop a full blown disorder had it not been for their exposure to high levels of food borne excitotoxin additives. Some may have had a very mild form of the disease had it not been for the exposure.

In July, 1995 the Federation of American Societies for Experimental Biology (FASEB) conducted a definitive study for the FDA on the question of safety of MSG. The FDA wrote a very deceptive summery of the report in which they implied that, except possibly for asthma patients, MSG was found to be safe by the FASEB reviewers. But, in fact, that is not what the report said at all. I summarized, in detail, my criticism of this widely reported FDA deception in the revised paperback edition of my book, Excitotoxins: The Taste That Kills, by analyzing exactly what the report said, and failed to say. For example, it never said that MSG did not aggravate neurodegenerative diseases. What they said was, there were no studies indicating such a link. Specifically, that no one has conducted any studies, positive or negative, to see if there is a link. In other words it has not been looked at. A vital difference.

Unfortunately, for the consumer, the corporate food processors not only continue to add MSG to our foods but they have gone to great links to disguise these harmful additives. For example, they use such names a hydrolyzed vegetable protein, vegetable protein, hydrolyzed plant protein, caseinate, yeast extract, and natural flavoring. We know experimentally, as stated, when these

excitotoxin taste enhancers are added together they become much more toxic. In fact, excitotoxins in subtoxic concentrations can be fully toxic to specialized brain cells when used in combination. Frequently, I see processed foods on supermarket shelves, especially frozen of diet food, that contain two, three or even four types of excitotoxins. We also know that excitotoxins in a liquid form are much more toxic than solid forms because they are rapidly absorbed and attain high concentration in the blood. This means that many of the commercial soups, sauces, and gravies containing MSG are very dangerous to nervous system health, and should especially be avoided by those either having one of the above mentioned disorders, or are at a high risk of developing one of them. They should also be avoided by cancer patients and those at high risk for cancer.

In the case of ALS, amyotrophic lateral sclerosis, we know that consumption of red meats and especially MSG itself, can significantly elevate blood glutamate, much higher than is seen in the normal population. Similar studies, as far as I am aware, have not been conducted in patients with Alzheimer's disease or Parkinson's disease. But, as a general rule I would certainly suggest that person's with either of these diseases avoid MSG containing foods as well as red meats, cheeses, and pureed tomatoes, all of which are known to have high levels of glutamate.

It must be remembered that it is the glutamate molecule that is toxic in MSG (monosodium glutamate). Glutamate is a naturally occurring amino acid found in varying concentrations in many foods. Defenders of MSG safety allude to this fact in their defense. But, it is free glutamate that is the culprit. Bound glutamate, found naturally in foods, is less dangerous because it is slowly broken down and absorbed by the gut, so that it can be utilized by the tissues, especially muscle, before toxic concentrations can build up. Therefore, a whole tomato is safer than a pureed tomato. The only exception to this, based on present knowledge, is in the case of ALS. Also, in the case of tomatoes, the plant contains several powerful antioxidants known to block glutamate toxicity.

Hydrolyzed vegetable protein should not be confused with hydrolysed vegetable oil. The oil does not contain appreciable concentration of glutamate, it is an oil. Hydrolyzed vegetable protein is made by a chemical process that breaks down the vegetable's protein structure to purposefully free the glutamate, as well as aspartate, another excitotoxin. This brown powdery substance is used to enhance the flavor of foods, especially meat dishes, soups, and sauces. Despite the fact that some health food manufacturers have attempted to sell the idea that this flavor enhancer is " all natural" and "safe" because it is made from vegetables, it is not. It is the same substance added to processed foods. Experimentally, one can produce the same brain lesions using hydrolyzed vegetable protein as by using MSG or aspartate.

A growing list of excitotoxins is being discovered, including several that are found naturally. For example, L- cysteine is a very powerful excitotoxin. Recently, it has been added to certain bread dough and is sold in health food stores as a supplement. Homocysteine, a metabolic derivative, is also an excitotoxin. Interestingly, elevated blood levels of homocysteine has recently been shown to be a major, if not the major, indicator of cardiovascular disease and stroke. Equally interesting, is the finding that elevated levels have also been implicated in neurodevelopmental disorders, especially anencephaly and spinal dysraphism (neural tube defects). It is thought that this is the protective mechanism of action of the prenatal vitamins B12, B6, and folate when used in combination. It remains to be seen if the toxic effect is excitatory or by some other mechanism. If it is excitatory, then unborn infants would be endangered as well by glutamate, aspartate (part of the aspartame molecule), and the other excitotoxins. Recently, several studies have been done in which it was found that all Alzheimer's patients examined had elevated levels of homocysteine.

Recent studies have shown that persons affected by Alzheimer's disease also have widespread destruction of their retinal ganglion cells. Interestingly, this is the area found to be affected when Lucas and Newhouse first discovered the excitotoxicity of MSG. While this does not prove that dietary glutamate and other excitotoxins cause or aggravate Alzheimer's disease, it makes one very suspicious. One could argue a common intrinsic etiology for central nervous system

neuronal damage and retinal ganglion cell damage, but these findings are disconcerting enough to warrant further investigations.

The Free Radical Connection

It is interesting to note that many of the same neurological diseases associated with excitotoxic injury are also associated with accumulations of toxic free radicals and destructive lipid enzymes. For example, the brains of Alzheimer's disease patients have been found to contain high concentration of lipolytic enzymes, which seems to indicate accelerated membrane lipid peroxidation, again caused by free radical generation.

In the case of Parkinson's disease, we know that one of the early changes is the loss of glutathione from the neurons of the striate system, especially in a nucleus called the substantia nigra. It is this nucleus that is primarily affected in this disorder. Accompanying this, is an accumulation of free iron, which is one of the most powerful free radical generators known. One of the highest concentrations of iron in the body is within the globus pallidus and the substantia nigra. The neurons within the latter are especially vulnerable to oxidant stress because the oxidant metabolism of the transmitter-dopamine- can proceed to the creation of very powerful free radicals. That is, it can auto-oxidize to peroxide,which is normally detoxified by glutathione. As we have seen, glutathione loss in the substantia nigra is one of the earliest deficiencies seen in Parkinson's disease. In the presence of high concentrations of free iron, the peroxide is converted into the dangerous, and very powerful free radical, hydroxide. As the hydroxide radical diffuses throughout the cell, destruction of the lipid components of the cell takes place, a process called lipid peroxidation.

Using a laser microprobe mass analyzer, researchers have recently discovered that iron accumulation in Parkinson's disease is primarily localized in the neuromelanin granules (which gives the nucleus its black color). It has also been shown that there is dramatic accumulation of aluminum within these granules. Most likely, the aluminum displaces the bound iron, releasing highly reactive free iron. It is known that even low concentrations of aluminum salts can enhance iron-induced lipid peroxidation by almost an order of magnitude. Further, direct infusion of iron into the substantia nigra nucleus in rodents can induce a Parkinsonian syndrome, and a dose related decline in dopamine. Recent studies indicate that individuals having Parkinson's disease also have defective iron metabolism.

Another early finding in Parkinson's disease is the reduction in complex I enzymes within the mitochondria of this nucleus. It is well known that the complex I enzymes are particularly sensitive to free radical injury. These enzymes are critical to the production of cellular energy. When cellular energy is decreased, the toxic effect of excitatory amino acids increases dramatically, by as much as 200 fold. In fact, when energy production is very low, even normal concentrations of extracellular glutamate and aspartate can kill neurons.

One of the terribly debilitating effects of Parkinson's disease is a condition called " freezing up", a state where the muscle are literally frozen in place. There is recent evidence that this effect is due to the unopposed firing of a special nucleus in the brain (the subthalamic nucleus). Interestingly, this nucleus uses glutamate for its transmitter. Neuroscientists are exploring the use of glutamate blocking drugs to prevent this disorder.

And finally, there is growing evidence that similar free radical damage, most likely triggered by toxic concentrations of excitotoxins, causes ALS. Several studies have demonstrated lipid peroxidation product accumulation within the spinal cords of ALS victims. Iron accumulation has also been seen in the spinal cords of ALS victims.

Besides the well known reactive oxygen species, such as super oxide, hydroxyl ion, hydrogen peroxide, and singlet oxygen, there exist a whole spectrum of reactive nitrogen species derived from nitric oxide, the most important of which is peroxynitrate. These free radicals can attack

proteins, membrane lipids and DNA, both nuclear and mitochondrial, which makes these radicals very dangerous.

It is now known that glutamate acts on its receptor via a nitric oxide mechanism.Overstimulation of the glutamate receptor can result in accumulation of reactive nitrogen species, resulting in the concentration of several species of dangerous free radicals. There is growing evidence that, at least in part, this is how excess glutamate damages nerve cells. In a multitude of studies, a close link has been demonstrated between excitotoxity and free radical generation. Others have shown that certain free radical scavengers (anti-oxidants), have successfully blocked excitotoxic destruction of neurons. For example, vitamin E is known to completely block glutamate toxicity in vitro (in culture). Whether it will be as efficient in vivo (in a living animal) is not known. But, it is interesting in light of the recent observations that vitamin E slows the course of Alzheimer's disease, as had already been demonstrated in the case of Parkinson's disease. There is some clinical evidence, including my own observations, that vitamin E also slows the course of ALS as well, especially in the form of D-Alpha-tocopherol. I would caution that anti-oxidants work best in combination and when use separately can have opposite, harmful, effects. That is, when antioxidants, such as ascorbic acid and alpha tocopherol, become oxidized themselves, such as in the case of dehydroascorbic acid, they no longer protect, but rather act as free radicals themselves. The same is true of alpha-tocopherol.

We know that there are four main endogenous sources of oxidants:

1. Those produced naturally from aerobic metabolism of glucose.
2. Those produced during phagocytic cell attack on bacteria, viruses, and parasites, especially with chronic infections.
3. Those produced during the degradation of fatty acids and other molecules that produce H2O2 as a by-product. (This is important in stress, which has been shown to significantly increase brain levels of free radicals.)
4. Oxidants produced during the course of p450 degradation of natural toxins.

And, as we have seen, one of the major endogenous sources of free radicals is from exposure to free iron. Unfortunately, iron is one mineral heavily promoted by the health industry, and is frequently added to many foods, especially breads and pastas. Copper is also a powerful free radical generator and has been shown to be elevated within the substantia nigra nucleus of Parkinsonian brains.

When free radicals are generated, the first site of damage is to the cell membranes, since they are composed of polyunsaturated fatty acid molecules known to be highly susceptible to such attack. The process of membrane lipid oxidation is known as lipid peroxidation and is usually initiated by the hydroxal radical. We know that one's diet can significantly alter this susceptibility. For example, diets high in omega 3-polyunsaturated fatty acids (fish oils and flax seed oils) can increase the risk of lipid peroxidation experimentally. Contrawise, diets high in olive oil, a monounsaturtated oil, significantly lowers lipid peroxidation risk. From the available research. the beneficial effects of omega 3-fatty acid oils in the case of strokes and heart attacks probably arises from the anticoagulant effect of these oils and possibly the inhibition of release of arachidonic acid from the cell membrane. But, olive oil has the same antithrombosis effect and anticancer effect but also significantly lowers lipid peroxidation.

The Blood-Brain Barrier

One of the MSG industry's chief arguments for the safety of their product is that glutamate in the blood cannot enter the brain because of the blood-brain barrier (BBB), a system of specialized capillary structures designed to exclude toxic substance from entering the brain. There are several criticisms of their defense. For example, it is known that the brain, even in the adult, has several areas that normally do not have a barrier system, called the circumventricular organs. These include the hypothalamus, the subfornical organ, organium vasculosum, area postrema,

pineal gland, and the subcommisural organ. Of these, the most important is the hypothalamus, since it is the controlling center for all neuroendocrine regulation, sleep wake cycles, emotional control, caloric intake regulation, immune system regulation and regulation of the autonomic nervous system. Interestingly, it has recently been found that glutamate is the most important neurotransmitter in the hypothalamus. Therefore, careful regulation of blood levels of glutamate is very important, since high blood concentrations of glutamate can easily increase hypothalamic levels as well. One of the earliest and most consistent findings with exposure to MSG is damage to an area known as the arcuate nucleus. This small hypothalamic nucleus controls a multitude of neuroendocrine functions, as well as being intimately connected to several other hypothalamic nuclei. It has also been demonstrated that high concentrations of blood glutamate and aspartate (from foods) can enter the so-called “protected brain” by seeping through the unprotected areas, such as the hypothalamus or circumventricular organs.

Another interesting observation is that chronic elevations of blood glutamate can even seep through the normal blood-brain barrier when these high concentrations are maintained over a long period of time. This, naturally, would be the situation seen when individuals consume, on a daily basis, foods high in the excitotoxins - MSG, aspartame and cysteine. Most experiments cited by the defenders of MSG safety were conducted to test the efficiency of the BBB acutely. In nature, except in the case of metabolic dysfunction (Such as with ALS), glutamate and aspartate levels are not normally elevated on a daily basis. Sustained elevations of these excitotoxins are peculiar to the modern diet. (And in the ancient diets of the Orientals, but not in as high a concentration.)

An additional critical factor ignored by the defenders of excitotoxin food safety is the fact that many people in a large population have disorders known to alter the permeability of the blood-brain barrier. The list of condition associated with barrier disruption include: hypertension, diabetes, mini-strokes, major strokes, head trauma, multiple sclerosis, brain tumors, chemotherapy, radiation treatments to the nervous system, collagen-vascular diseases (lupus), AIDS, brain infections, certain drugs, Alzheimer’s disease, and as a consequence of natural aging. There may be many other conditions also associated with barrier disruption that are as yet not known.

When the barrier is dysfunctional due to one of these conditions, brain levels of glutamate and aspartate reflect blood levels. That is, foods containing high concentrations of these excitotoxins will increase brain concentrations to toxic levels as well. Take for example, multiple sclerosis. We know that when a person with MS has an exacerbation of symptoms, the blood-brain barrier near the lesions breaks down, leaving the surrounding brain vulnerable to excitotoxin entry from the blood, i.e. the diet. But, not only is the adjacent brain vulnerable, but the openings act as a points of entry, eventually exposing the entire brain to potentially toxic levels of glutamate. Several clinicians have remarked on seeing MS patients who were made worse following exposure to dietary excitotoxins. I have seen this myself.

It is logical to assume that patients with the other neurodegenerative disorders, such as Alzheimer’s disease, Parkinson’s disease, and ALS will be made worse on diets high in excitotoxins. Barrier disruption has been demonstrated in the case of Alzheimer’s disease.

Recently, it has been shown that not only can free radicals open the blood-brain barrier, but excitotoxins can as well. In fact, glutamate receptors have been demonstrated on the barrier itself. In a carefully designed experiment, researchers produced opening of the blood-brain barrier using injected iron as a free radical generator. When a powerful free radical scavenger (U-74006F) was used in this model, opening of the barrier was significantly blocked. But, the glutamate blocker MK-801 acted even more effectively to protect the barrier. The authors of this study concluded that glutamate appears to be an important regulator of brain capillary transport and stability, and that overstimulation of NMDA (glutamate) receptors on the blood-brain barrier appears to play an important role in breakdown of the barrier system. What this also means is

that high levels of dietary glutamate or aspartate may very well disrupt the normal blood-brain barrier, thus allowing more glutamate to enter the brain, sort of a vicious cycle.

Relation to Cellular Energy Production

Excitotoxin damage is heavily dependent on the energy state of the cell. Cells with a normal energy generation systems that are efficiently producing adequate amounts of cellular energy, are very resistant to such toxicity. When cells are energy deficient, no matter the cause - hypoxia, starvation, metabolic poisons, hypoglycemia - they become infinitely more susceptible to excitotoxic injury or death. In fact, even normal concentrations of glutamate are toxic to energy deficient cells.

It is known that in many of the neurodegenerative disorders, neuron energy deficiency often precedes the clinical onset of the disease by years, if not decades. This has been demonstrated in the case of Huntington disease and Alzheimer's disease using the PET scanner, which measures brain metabolism. In the case of Parkinson's disease, several groups have demonstrated that one of the early deficits of the disorder is an impaired energy production by the complex I group of enzymes from the mitochondria of the substantia nigra. (Part of the Electron Transport System.) Interestingly, it is known that the complex I system is very sensitive to free radical damage.

Recently, it has been shown that when striatal neurons (those involved in Parkinson's and Huntington's diseases.) are exposed to microinjected excitotoxins there is a dramatic, and rapid fall in energy production by these neurons. CoEnzyme Q10 has been shown, in this model, to restore energy production but not to prevent cellular death. But when combined with niacinamide, both cellular energy production and neuron protection is seen. I would recommend for those with neurodegenerative disorders, a combination of CoQ10, acetyl-L carnitine, niacinamide, riboflavin, methylcobalamin, and thiamine.

One of the newer revelations of modern molecular biology is the discovery of mitochondrial diseases, of which cellular energy deficiency is a hallmark. In many of these disorders, significant clinical improvement has been seen following a similar regimen of vitamins combined with CoQ10 and L-carnitine. Acetyl L-carnitine enters the brain in higher concentrations and also increases brain acetylcholine, necessary for normal memory function. While these particular substances have been found to significantly boost brain energy function they are not alone in this important property. Phosphotidyl serine, Ginkgo Biloba, vitamin B12, folate, magnesium, Vitamin K and several others are also being shown to be important.

While mitochrondial dysfunction is important in explaining why some are more vulnerable to excitotoxin damage than others, it does not explain injury in those with normal cellular metabolism. There are several conditions under which energy metabolism is impaired. For example, approximately one third of Americans suffer from what is known as reactive hypoglycemia. That is, they respond to a meal composed of either simple sugars or carbohydrates that are quickly broken down into simple sugars (a high glycemic index.) by secreting excessive amounts of insulin. This causes a dramatic lowering of the blood sugar.

When the blood sugar falls, the body responds by releasing a burst of epinephrine from the adrenal glands, in an effort to raise the blood sugar. We feel this release as nervousness, palpitations of our heart, tremulousness, and profuse sweating. Occasionally, one can have a slower fall in the blood sugar that will not produce a reactive release of epinephrine, thereby producing few symptoms. This can be more dangerous, since we are unaware that our glucose reserve is falling until we develop obvious neurological symptoms, such as difficulty thinking and a sensation of lightheadedness.

The brain is one of the most glucose dependent organs known, since it has a limited ability to burn other substrates such as fats. There is some evidence that several of the neurodegenerative

diseases are related to either excessive insulin release, as with Alzheimer's disease, or impaired glucose utilization, as we have seen in the case of Parkinson's disease and Huntington's disease.

It is my firm belief, based on clinical experience and physiological principles, that many of these diseases occur primarily in the face of either reactive hypoglycemia or " brain hypoglycemia". In at least two well conducted studies it was found that pure Alzheimer's dementia was rare in those with normal blood sugar profiles, and that in most cases Alzheimer's patients had low blood sugars, and high CSF (cerebrospinal fluid) insulin levels. In my own limited experience with Parkinson's and ALS patients I have found a disproportionately high number suffering from reactive hypoglycemia.

I found it interesting that several ALS patients have observed an association between their symptoms and gluten. That is, when they adhere to a gluten free diet they improve clinically. It may be that by avoiding gluten containing products, such as bread, crackers, cereal, pasta, etc, they are also avoiding products that are high on the glycemic index, i.e. that produce reactive hypoglycemia. Also, all of these food items are high in free iron. Clinically, hypoglycemia will worsen the symptoms of most neurological disorders. We know that severe hypoglycemia can, in fact, mimic ALS both clinically and pathologically. It is also known that many of the symptoms of Alzheimer's disease resemble hypoglycemia, as if the brain is hypoglycemic in isolation.

In studies of animals exposed to repeated mild episodes of hypoxia (lack of brain oxygenation), it was found that such accumulated injuries can trigger biochemical changes that resemble those seen in Alzheimer's patients. One of the effects of hypoxia is a massive release of glutamate into the space around the neuron. This results in rapid death of these sensitized cells. As we age, the blood supply to the brain is frequently impaired, either because of atherosclerosis or repeated syncopal episodes, leading to short periods of hypoxia. Hypoglycemia produces lesions very similar to hypoxia and via the same glutamate excitotoxic mechanism. In fact, recent studies of diabetics suffering from repeated episodes of hypoglycemia associated with over medication with insulin, demonstrate brain atrophy and dementia.

Again, it should be realized that excessive glutamate stimulation triggers a chain of events that in turn triggers the generation of large numbers of free radical species, both as nitrogen species and oxygen species. Once this occurs, especially with the accumulation of the hydroxyl ion, destruction of the lipid components of the membranes occurs, as lipid peroxidation. In addition, these free radicals damage proteins and DNA as well. The most immediate DNA damage is to the mitochondrial DNA, which controls protein expression within that particular cell and its progeny. It is suspected that at least some of the neurodegenerative diseases, Parkinson's disease in particular, are inherited in this way. But more importantly, it may be that accumulated damage to the mitochondrial DNA secondary to progressive free radical attack (somatic mitochondrial injury) is the cause of most of the neurodegenerative diseases that are not inherited. This would result from an impaired reserve of antioxidant vitamins/minerals and enzymes, increased cellular stress, chronic infection, free radical generating metals and toxins, and impaired DNA repair enzymes.

It is estimated that the number of oxidative free radical injuries to DNA number about 10,000 a day in humans. Normally, these injuries are repaired by special repair enzymes. It is known that as we age these repair enzymes decrease or become less efficient. Also, some individuals are born with deficient repair enzymes from birth as, for example, in the case of xeroderma pigmentosum. Recent studies of Alzheimer's patients also demonstrate a significant deficiency in DNA repair enzymes and high levels of lipid peroxidation products in the affected parts of the brain. It is also important to realize that the hippocampus of the brain, most severely damaged in Alzheimer's dementia, is one of the most vulnerable areas of the brain to low glucose supply as well as low oxygen supply. That also makes it very susceptible to glutamate toxicity.

Another interesting finding is that when cells are exposed to glutamate they develop certain inclusions (cellular debris) that not only resembles the characteristic neurofibrillary tangles of

Alzheimer's dementia, but are immunologically identical as well. Similarly, when experimental animals are exposed to the chemical MPTP, they not only develop Parkinson's disorder, but the older animals develop the same inclusions (Lewy bodies) as see in human Parkinson's.

Eicosanoids and Excitotoxins

It is known that one of the destructive effects triggered by excitotoxins is the release of arachidonic acid from the cell membrane and the initiation of the eicosanoid reactions. Remember, glutamate primarily acts by opening the calcium pore, allowing calcium to pour into the cell's interior. Intracellular calcium in high concentrations initiates the enzymatic release of arachidonic acid from the cell membrane, where it is then attacked by two enzymes systems, the cyclooxygenase system and the lipooxgenase system. These in turn produce a series of compounds that can damage cell membranes, proteins and DNA, primarily by free radical production, but also directly by the "harmful eicosanoids."

Biochemically, we know that high glycemic carbohydrate diets, known to stimulate the excess release of insulin, can trigger the production of "harmful eicosanoids." We should also recognize that simple sugars are not the only substances that can trigger the release of insulin. One of the more powerful triggers includes certain amino acids, including leucine, alanine, and taurine. Glutamine, while not acting as an insulin trigger itself, markedly potentiates insulin release by leucine. This is why, except under certain situations, individual "free" amino acids should be avoided.

It is known that excitotoxins can also stimulate the release of these "harmful eicosanoids." So that in the situation of a hypoglycemic individual, they would be subjected to production of harmful eicosanoids directly by the high insulin levels, as well as by elevated glutamate levels. Importantly, both of these events significantly increase free radical production and hence, lipid peroxidation of cellular membranes. It should be remembered that diets high in arachidonic acid, such as egg yellows, organs meats, and liver, may be harmful to those subjected to excessive excitotoxin exposure.

And finally, in one carefully conducted experiment, it was shown that insulin significantly increases glutamate toxicity in cortical cell cultures and that this magnifying effect was not due to insulin's effect on glucose metabolism. That is, the effect was directly related to insulin interaction with cell membranes. Interestingly, insulin increased toxic sensitivity to other excitotoxins as well.

The Special Role of Flavanoids

Flavonoids are diphenylpropanoids found in all plant foods. They are known to be strong antioxidants and free radical scavengers. There are three major flavonols - quercetin, Kaempferol, and myricetin, and two major flavones - luteolin and apigenin. Seventy percent of the flavonoids intake in the average diet consist of quercetin, the main source of which is tea (49%), onions (29%), and apples (7%). Fortunately, flavonoids are heat stable, that is, they are not destroyed during cooking. Other important flavonoids include catechin, leucoanthocyanidins, anthocyanins, hesperedin and naringenin.

Most interest in the flavonoids stemmed from their ability to inhibit tumor initiation and growth. This was especially true of quercetin and naringenin, but also seen with hesperetin and the isoflavone, genistein. There appears to be a strong correlation between their anticarcinogenic potential and their ability to squelch free radicals. But, in the case of genistein and quercetin, it also has to do with their ability to inhibit tyrosine kinase and phosphoinositide phosphorylase, both necessary for mammary cancer and glioblastoma (a highly malignant brain tumor) growth and development.

As we have seen, there is a close correlation between insulin, excitotoxins, free radicals and eicosanoid production. Of particular interest, is the finding that most of the flavonoids, especially

quercetin, are potent and selective inhibitors of delta-5-lipooxygenase enzyme which initiates the production of eicosanods. Flavones are also potent and selective inhibitors of the enzyme cyclooxygenase (COX) which is responsible for the production of thromboxane A2, one of the "harmful eicosanoids". The COX-2 enzymes are associated only with excitatory type neurons in the brain and appears to play a major role in neurodegeneration.

One of the critical steps in the production of eicosanoids is the liberation of arachidonic acid from the cell membrane by phospholipase A2. Flavonones such as naringenin (from grapefruits) and hesperetin (citrus fruits) produce a dose related inhibition of phospholipase A2 (80% inhibition), thereby inhibiting the release of arachidonic acid. The non-steroidal anti-inflammatory drugs act similarly to block the production of inflammatory eicosanoids.

What makes all of this especially interesting is that recently, two major studies have found that not only can non-steroidal anti-inflammatories slow the course of Alzheimer's disease, but they may prevent it as well. But, these drugs can have significant side effects, such as GI bleeding, liver and kidney damage. In high doses, the flavonoids have shown a similar ability to reduce "harmful eicosanoid" production and should have the same beneficial effect on the neurodegenerative diseases without the side effects. Also, these compounds are powerful free radical scavengers and would be expected to reduce excitotoxicity as well.

But, there is another beneficial effect. There is experimental, as well as clinical evidence, that the flavonoids can reduce capillary leakage and strengthen the blood brain barrier. This has been shown to be true for rutin, hesperedin and some chalcones. Rutin and hesperedin have also been shown to strengthen capillary walls. In the form of hesperetin methyl chalcone, the hesperedin molecule is readily soluble in water, significantly increasing its absorbability. Blackcurrents have the highest concentration of hesperetin of any fresh fruit, and in a puree form, is even more potent.

The importance of these compounds again emphasizes the need for high intakes of fruits and vegetables in the diet, and may explain the low incidence of many of these disorders in strict vegetarians, since this would supply a high concentration of flavonoids, carotenoids, vitamins, minerals, and other antioxidants to the body. Normally, the flavonoids from fruits and vegetables are only incompletely absorbed, so that relatively high concentrations would be needed to attain the same therapeutic levels seen in these experiments. Juice Plus allows us to absorb high, therapeutic concentrations of these flavonoids by a process called cryodehydration. This process removes the water and sugar from fruits and vegetable but retains their flavonoids in a fully functional state. Also the process allows one to consume large amounts of fruits and vegetables that would be impossible with the whole plant.

Iron and Health

For decades we, especially women, have been told that we need extra iron for health -that it builds healthy blood. But, recent evidence indicates that iron and copper may be doing more harm than good in most cases. It has been well demonstrated that iron and copper are two of the most powerful generators of free radicals. This is because they catalyze the conversion of hydrogen peroxide into the very powerful and destructive hydroxyl radical. It is this radical that does so much damage to membrane lipids and DNA bases within the cell. It also plays a major role in the oxidation of LDL-cholesterol, leading to heart attacks and strokes.

Males begin to accumulate iron shortly after puberty and by middle age have 1000mg of stored iron in their bodies. Women, by contrast, because of menstruation, have only 300 mg of stored iron. But, after menopause they begin to rapidly accumulate iron so that by middle age they have about 1500 mg of stored iron. It is also known that the brain begins to accumulate iron with aging. Elevated iron levels are seen with all of the neurodegenerative diseases, such as Alzheimer's dementia, Parkinson's disease, and ALS. It is thought that this iron triggers free radical production within the areas of the brain destroyed by these diseases. For example, the part of the brain

destroyed by Parkinson's disease, the substantia nigra, has very high levels of free iron.

Normally, the body goes to great trouble to make sure all iron and copper in the body is combined to a special protein for transport and storage. But, with several of these diseases, we see a loss of these transport and storage proteins. This is where flavonoids come into play. We know that many of the flavonoids (especially quercitin, rutin, hesperidin, and naringenin) are strong chelators of iron and copper. In fact, drinking iced tea with a meal can reduce iron absorption by as much as 87%. But, flavonoids in the diet will not make you iron deficient.

Phosphotidyl serine and Excitotoxity

Recent clinical studies indicate that phophotidyl serine can significantly improve the mental functioning of a significant number of Alzheimer's patients, especially during the early stages of the disease. We know that the brain normally contains a large concentration of phosphotidyl serine. Interestingly, this compound has a chemical structure similar to L-glutamate, the main excitatory neurotransmitter in the brain. Binding studies show that phosphotidyl serine competes with L-glutamate for the NMDA type glutamate receptor. What this means is that phosphotidyl serine is a very effective protectant against glutamate toxicity. Unfortunately, it is also very expensive.

The Many Functions of Ascorbic Acid

The brain contains one of the highest concentrations of ascorbic acid in the body. Most are aware of its function in connective tissue synthesis and as a free radical scavenger. But, ascorbic acid has other functions that make it rather unique. Ascorbic acid in solution is a powerful reducing agent where it undergoes rapid oxidation to form dehydroascorbic acid. Oxidation of this compound is accelerated by high ph, temperature and some transitional metals, such as iron and copper. The oxidized form of ascorbic acid can promote lipid peroxidation and protein damage. This is why it is vital that you take antioxidants together, since several, such as vitamin E (as D-alpha-tocopherol) and alpha-lipoic acid, act to regenerate the reduced form of the vitamin.

In man, we know that certain areas of the brain have very high concentrations of ascorbic acid, such as the nucleus accumbens and hippocampus. The lowest levels are seen in the substantia nigra. These levels seem to fluctuate with the electrical activity of the brain. Amphetamine acts to increase ascorbic acid concentration in the corpus striatum (basal ganglion area) and decrease it in the hippocampus, the memory imprint area of the brain. Ascorbic acid is known to play a vital role in dopamine production as well.

One of the more interesting links has been between the secretion of the glutamate neurotransmitter by the brain and the release of ascorbic acid into the extracellular space. This release of ascorbate can also be induced by systemic administration of glutamate or aspartate, as would be seen in diets high in these excitotoxins . The other neurotransmitters do not have a similar effect on ascorbic acid release. This effect appears to be an exchange mechanism. That is, the ascorbic acid and glutamate exchange places. Theoretically, high concentration of ascorbic acid in the diet could inhibit glutamate release, lessening the risk of excitotoxic damage. Of equal importance is the free radical neutralizing effect of ascorbic acid.

There is now substantial evidence that ascorbic acid modulates the electrophysiological as well as behavioral functioning of the brain. It also attenuates the behavioral response of rats exposed to amphetamine, which is known to act through an excitatory mechanism. In part, this is due to the observed binding of ascorbic acid to the glutamate receptor. This could mean that ascorbic acid holds great potential in treating disease related to excitotoxic damage. Thus far, there are no studies relating ascorbate metabolism in neurodegenerative diseases. There is at least one report of ascorbic acid deficiency in guineas pigs producing histopathological changes similar to ALS.

It is known that as we age there is a decline in brain levels of ascorbic acid. When accompanied

by a similar decrease in glutathione peroxidase, we see an accumulation of H202 and hence, elevated levels of free radicals and lipid peroxidation. In one study it was found that with age not only does the extracellular concentration of ascorbic acid decrease but the capacity of the brain ascorbic acid system to respond to oxidative stress is impaired as well.

In terms of its antioxidant activity, vitamin C and E interact in such a way as to restore each others active antioxidant state. Vitamin C scavenges oxygen radicals in the aqueous phase and vitamin E in the lipid, chain breaking, phase. The addition of vitamin C suppresses the oxidative consumption of vitamin E almost totally, probably because in the living organism the vitamin C in the aqueous phase is adjacent to the lipid membrane layer containing the vitamin E.

When combined, the vitamin C was consumed faster during oxidative stress than the vitamin E. Once the vitamin C was totally consumed, the vitamin E began to be depleted at an accelerated rate. N-acetyl-L-cysteine and glutathione can reduce vitamin E consumption as well, but less effectively than vitamin C. The real danger is when vitamin C is combined with iron. Recent experiments have shown that such combinations can produce widespread destruction within the striate areas of the brain. This is because the free iron oxidizes the ascorbate to produce the powerful free radical hydroxyascorbate. Alpha-lipoic acid acts powerfully to keep the ascorbate and tocopherol in the reduced state (antioxidant state). As we age, we produce less of the transferrin transport protein that normally binds free iron. As a result, older individuals have higher levels of free iron within their tissues, including brain.

Conclusion

In this discussion, I tried to highlight some of the more pertinent of the recent findings related to excitotoxicity in general and neurodegenerative diseases specifically. In no way is this an all inclusive discussion of this topic. There are many areas I had to omit because of space, such as alpha-lipoic acid, an antioxidant that holds great promise in combatting many of these diseases. Also, I did not go into detail concerning the metabolic stimulants, the relationship between exercise and degenerative nervous system diseases, the protective effect of methycobalamin, and the various disorders related to excitotoxins.

I also purposely omitted discussions of magnesium to keep this paper short. It is my experience, that magnesium is one of the most important neuroprotectants known. I would encourage those who suffer from one of the excitotoxin related disorders to avoid, as much as possible, food borne excitotoxin additives and to utilize the substances discussed above. The fields of excitotoxin research, in combination with research on free radicals and eicosanoids, are growing very rapidly and new information arises daily. Great promise exists in the field of flavonoid research as regards many of these neurodegenerative diseases as well as in our efforts to prevent neurodegeneration itself.

A recent study has demonstrated that aspartame feeding to animals results in an accumulation of formaldehyde within the cells, with evidence of significant damage to cellular proteins and DNA. In fact, the formaldehyde accumulated with prolonged use of aspartame. With this damning evidence, one would have to be suicidal to continue the use of aspartame sweetened foods, drinks and medicines. The use of foods containing excitotoxin additives is especially harmful to the unborn and small children. By age 4 the brain is only 80% formed. By age 8, 90% and by age 16 it is fully formed, but still undergoing changes and rewiring (plasticity). We know that the excitotoxins have a devastating effect on formation of the brain (wiring of the brain) and that such exposure can cause the brain to be "miswired." This may explain the significant, almost explosive increase in ADD and ADHD. Glutamate feeding to pregnant animals produces a syndrome almost identical to ADD. It has also been shown that a single feeding of MSG after birth can increase free radicals in the offspring’s brain that last until adolescence. Experimentally, we know that infants are 4X more sensitive to the toxicity of excitotoxins than are adults. And, of all the species studied, cats, dogs, primates, chickens, guinea pigs, and rats, humans are by far the most sensitive to glutamate toxicity. In fact, they are 5x more sensitive than rats and 20x more

sensitive than non-human primates.

I have been impressed with the dramatic improvement in children with ADD and ADHD following abstention from excitotoxin use. It requires care monitoring of these children. Each time they are exposed to these substances, they literally go bonkers. It is ludicrous, with all we know about the destructive effects of excitotoxins, to continue to allow ourselves and our children to continue on this destructive path.

Fran

Fran,

You get the prize for the longest post. Thank God you didn't include Mg.

I think it's worth repeating that the hypothalamus and pituitary as well as parts of the brainstem immediately adjacent to the ventricular system (contains cerebrospinal fluid) do not have a blood brain barrier. Hence, they have no protection against free glutamate.

PC

Hello Fran,

That was a most enlightening article that I will share with many. Thank you for diligently searching and finding this info. I know how much time it takes, to just find one thing of interest. This was a gold mine.

I must share a funny story that happened a week ago that pertains to this article and is one of life's strange synchronicities. My wife and I are both researching every free moment we get, so we are both in tune. Rhonda was tired, so went to take a late morn nap, as she is studying late into the night and gets up at 6am with the kids for school. She got up from her nap and had been having dreams about researching and one thing stood out. She was told in her dream "Tony's extract". So we both laughed when she decided to go on the computer to see if there was an extract by this name. There was no extract, but there was Tony Crisp's extract, on the third line down. He was also someone who specialized in dreams and felt how important it was to take grapefruit seed extract. That was Tony's extract. So my wife has been on a search to find a good source, since our local health food store does not carry it. It struck me strange, when reading your article and the reference made to grapefruit flavonoids, which I know to be in the membranes of citrus, but don't know if there in the seeds. I do know, however, that the seeds of any fruits are good for us, as they contain the energy source for the plant and have many important fatty acids, so when you juice those oranges, make sure you consume the membranes and seeds.

Much respect and many thanks,

Richard V57 (I decided to add)

Fran, thank you for telling me about this spot, this is a fascinating discussion. I only have one question. I'd like to try and get some of these additives through diet if possible, are there any foods that are particularly strong in B6 and the rest?

Katy

There are a couple of books on Excitotoxins one by the author of this article - Russell L Blaylock - "Excitotoxins - The Taste That Kills at Amazon".

Kent

Fellow Fibbers,

Because I wanted you to know that I haven't dropped the ball (yet), I thought another speculative post was in order.

Since taking large doses of P5P, I've noticed that not only have my HR and HRV been frame shifted (as previously posted) but also that I get "hunger pangs" and borborygmi (fancy talk to describe a talking gut). I've wondered about this for the last week or so and have come up with the following (please overlook the technical language, as most of it has been lifted from the pertinent hyperlink):

Part I
Glutamic acid decarboxylase (=GAD), which catalyzes formation of GABA from glutamate, is detectable in different isoforms with distinct electrophoretic and kinetic characteristics. These two isoforms are found in the brain and in the beta cells of the pancreas. That in the brain is known as GAD 67 (encoded by gene GAD1) and that in the pancreas is GAD 65 (encoded by gene GAD2). Both are targets of autoantibodies in people who later develop insulin-dependent (Type I) diabetes mellitus (IDDM; 222100). Von Boehmer and Sarukhan (1999) suggested that GAD is the initiating autoantigen in human type I diabetes because GAD-specific autoantibodies are among the first to appear in the prediabetic phase in human patients. De Aizpurua et al. (1992) demonstrated that autoantibody against GAD was present in most subjects defined as having preclinical IDDM and that pancreatic islet and brain GAD are probably crossreactive.
Among 1,122 patients with type II diabetes (125853), Tuomi et al. (1999) found GAD antibody in 9.3%, a significantly higher prevalence than that found in patients with impaired glucose tolerance or in controls. He suggested the designation latent autoimmune diabetes in adults (LADA) to define the subgroup of type II diabetes patients with GADab positivity and age at onset greater than 35 years.

GAD activity in beta islet cells (which also secrete insulin) down regulates glucagon secretion. This means that a GAD shortfall translates to excess secretion of glucagon and higher blood glucose levels, hence diabetes.

http://www.genome.ad.jp/dbget-bin/www_bget?omim+138275

This suggests that a mutation in GAD might have survival benefits wrt development of either Type I or II diabetes mellitus. The incidence of diabetes amongst LAFers, according to Hans' survey, suggests that this hypothesized mutation or polymorphism is quite successful.

Part II
Several different enzymes - all pyridoxal-dependent decarboxylases - seem to share regions of sequence similarity [1,2,3,4], especially in the vicinity of the lysine residue which serves as the attachment site for the pyridoxal- phosphate (PLP) group.

These enzymes are:

Glutamate decarboxylase (GAD). Catalyzes the decarboxylation of glutamate into the neurotransmitter GABA

Histidine decarboxylase (HDC). Catalyzes the decarboxylation of histidine to histamine.

Aromatic-L-amino-acid decarboxylase, also known as L-dopa decarboxylase (DDC) or tryptophan decarboxylase. DDC catalyzes the decarboxylation of tryptophan to tryptamine. It also acts on 5-hydroxy- tryptophan (serotonin) and dihydroxyphenylalanine (L-dopa).

Tyrosine decarboxylase (EC 4.1.1.25) (TyrDC) regulates tyrosine <-> tyramine

Cysteine sulfinic acid decarboxylase

L-2,4-diaminobutyrate decarboxylase (DABA decarboxylase).

These enzymes are collectively known as group II decarboxylases [3,4].

http://us.expasy.org/cgi-bin/nicedoc.pl?PDOC00329

All group II decarboxylases are low-abundance and unstable PLP-dependent enzymes with important physiological roles. Knowledge of structure±function relationships among these enzymes has been limited by the difficulties in isolating sufficient amounts of proteins for molecular studies.

http://www.biochemj.org/bj/320/0365/3200365.pdf

http://www3.ncbi.nlm.nih.gov/htbin-post/Entrez/query?uid=94237165&form=6&db=m&Dopt=b

What if this hypothesized polymorphism (selected for because of its protective effects wrt diabetes) were in the “attachment site for the pyridoxal- phosphate (PLP) group”? If such were the case, then all these enzymes might become problematic as diets deteriorated (less B6, less Mg).

The excess glutamate fits just about right for VMAF. My hunger pangs may have been secondary to increased histamine levels (mediate gastric acid secretion) and my talking gut may have been speaking on behalf of serotonin (mediates GI motility).

On the other hand we know tyramine to be a trigger for some AMAFers. I haven’t yet worked out the details on the enzymatic implications for catecholamines and glucocorticoids, but this scenario appears provocative. The fact that knowledge of molecular details of these very enzymes has been limited further underscores this possibility.

This information suggests that VMAF and AMAF may be more related than I initially thought.

PC

Hello PC,

I've been reading about cytochrome P450 and came across this article, and this is, in part, what it said:

www.uky.edu/Pharmacy/ps/porter/CPR_enzymology.htm

The interaction of CPR with cytochrome P450 and other electron acceptor proteins is based

primarily on electrostatic charge pairing, although there is evidence for an additional hydrophobic component.18 Chemical cross-linking and modification studies have shown that CPR contains multiple carboxylate groups, presumably contributed by the acidic amino acids aspartate and glutamate.19 These charge groups pair with basic amino acids (lysines, arginines) on the various electron acceptor proteins. In addition, cytochrome P450 forms a dipole across the molecule, with the positive charge at the proximal face of the protein where the heme makes its closest approach to the surface.20 This is thought to be the surface most suitable for electron transfer from CPR. While electrostatic forces may serve to connect and orient the pair, hydrophobic forces contributed by nonpolar amino acids (leucine, tryptophan, valine, and others) may be responsible for bringing the two proteins close enough together for electron transfer.18 Other electron acceptor proteins, such as cytochrome b5, heme oxygenase, and squalene monooxygenase probably interact by the same mechanism.21

Could it be that we don't have enough basic amino acids to pair with the acidic amino acids, hence free glutamate floating around? And then maybe we're low in the non-polar amino acids to even carry out the electron transfer. Have you done an amino acid panel on yourself?

Thanks,
Richard v57

PC

Your hypothesis fits with the article you posted about PRH if I remember correctly. Was it not them that said that atrial fibrillation was the body's way of protecting itself against insulin - or there abouts? So in a funny way it may be that AF is protection against worse things and that may be why I was not aware I had PRH until I stopped free glutamate and got rid of AF.

Richard

You and your girl are quite a team. Weird things like that happen to me too. Jackie knows about grapefruit seed extract. She wrote me an email before the new year telling me about it. In my haste of reading I read grape seeds and told her how I juiced them with my grapes (will not eat seedless grapes). For those on meds - remember that grape fruit can interact with many meds.

Fran

Oh boy!!!! More to read. Here are some studies on glutamate, some of which are very interesting.

http://jpet.aspetjournals.org/cgi/search?sendit=Search&pubdate_year=&volume=&firstpage=&DOI=&author1=&author2=&title=&andorexacttitle=and&titleabstract=&andorexacttitleabs=and&fulltext=glutamate&andorexactfulltext=and&fmonth=Aug&fyear=1965&tmonth=Apr&tyear=2003&hits=10&sortspec=relevance

Fran,

I did read that one of the enzymes of the cytochrome P450 used for metabolizing particular drugs was also used for metabolizing grapefruit. I don't think it effected me, but I'll double check. But others should know what enzyme of the P450 class, their drug either inhibits or uses for metabolization. Doctors prescribing conflicting medications of these enzymes, results in over a hundred-thousand deaths each year. Amiodarone uses and inhibits quite a few enzymes, and this might very well be the reason for such adverse side effects. These P450 enzymes, also play a

part in glutamate.

For those on meds, see my post on the BB to look up your drug and see what enzymes are involved.

Thanks Fran,

Richard v57

Richard,

Haven't done any amino acid tests. I'm afraid the results would confuse me even more than I already am.

Thanks again for the continuing input on sources of information. Really enjoyed that one that you found and to which I referred in my initial post on this topic.

PC

Fran,

"So in a funny way it may be that Af is protection against worse things and that may be why I was not aware I had PRH until I stopped free glutamate and got rid of AF."

I think that you are probably right in thinking that you didn't have PRH while you had VMAF. GLP-1 (more than the other incretins - GLP-2 and GIP) is responsible for enhanced insulin effect and decreased glucagon effect. Its secretion is stimulated by rapid gastric emptying. Magnesium increases gastric motility (in addition Mg deficiency causes difficulty swallowing and constipation, all due to smooth muscle dysmotility). When you had VMAF you were probably also Mg deficient. Gastric emptying was anything but rapid and this resulted in less GLP-1 (probably slowly downregulated over all those years of increasing Mg deficiency). With improvement in Mg and VMAF came more rapid gastric emptying. The post VMAF PRH is probably mediated by this subsequently increased GLP-1. Hopefully the GLP-1 will again be downregulated over time.

Just a thought.

For those unfamiliar with this discussion, please proceed to the Proceedings of the Conference Room and look under Hypoglycemia. GLP-1 is markedly increased in those with PRH (postprandial reactive hypoglycemia).

PC

Hi Katy

Organ meats are highest in B6 that I am aware of. So are fish. I have since learnt that any high glutamate foods will have a counter productive form of B6 in it. eg tomatoes. So when you eat non-commercial food your needs will naturally be balanced. Eating commercial and processed foods make a lot out of free glutamate as this is what makes the flavour and the B6 will be dead, so it is best to avoid these, that includes boxed cereals! B6 breaks down in cooking and storage so if you eat a lot of raw spinach, tomatoes, parsley, fish and liver (raw) if you can manage it you

will start building it up again.

Yeast extract is also high in B6. But it is also high in free glutamate. I try to avoid all sources of free glutamate as this is 20 times stronger than bound glutamate. However, last night I had some marmite on a teaspoon and licked it all off very slowly. I seem to be alright. The craving was over powering and I am also a strong believer in letting my body tell me of its needs.

Fran

Well if this is not the proof I have been looking for about a genetic problem in my family with Vit B6 I don't know what is. My sister has RA and here is the title of a paper entitled Plasma Pyridoxal 5'-Phosphate Concentration Is Correlated with Functional Vitamin B-6 Indices in Patients with Rheumatoid Arthritis and Marginal Vitamin B-6 Status. I suspect this in me but I got AF instead. Now I have to see if there is a correlation with this and unknown dementias. From Google there is 152 articles linking them together. Now why is it that it affects us all in such different ways. I have always felt that the diverse nature of our families ailments were linked. They are supposed to be hereditary in themselves. But no - we get different variations of the same thing. Does that make sense? Just rambling

Fran

Hi Fran,

Lets talk about red meat. I didn't realize glutamate was in it. Since being on the paleo-diet, I've been eating red meat(organic) 2-3 times a week. What do you think?

And...thanks so much for this article. I've printed it for my wife to read.

Jim

Jim

Luckily we do not need to worry so much about bound glutamate. eg in red meat. It is only when it is freed from its enzyme or protein chain that the imbalance sets in. Glutamate is freed by over cooking. So by eating red meat that is not over cooked we are all right. For that reason I do not tend to casserole or stew tough meat cuts. The cooking not only tenderises the meat, but breaks bound glutamate into free glutamate. When the body breaks down bound glutamate it forms free glutamate as an excitory neurotransmitter, GABA to inhibit it (with B6 etc).

I eat red meat maybe five or six times a week and have been fine. I avoid over cooked and over ripe tomatoes like the plague. Tomatoes have a natural free glutamate in them but they are also high in B6. When they are cooked or pureed the B6 is destroyed and the bound glutamate is made free and wham you have a glutamate hit - or Af in my book.

Hope that helps. It made all the difference in the world to me.

Fran

Jim

I suddenly realised you might be asking about red meat because of the ALS connection. It worried me to in the beginning. I felt I had symptoms of ALS. However, with the dramatic improvement of avoiding free glutamate I do not get symptoms of ALS anymore. Red meat makes me feel steady. I now think, and understand from various research reports that neurotoxins can make the body mimic many diseases - such as MS, ALS, RA, dementia's etc.

If you think you do have ALS then it would be wise to avoid them. I would also ask to be checked out for it. But see how you feel after omitting free glutamate. Seemingly aspirin is a glutamate blocking drug but I think for the amounts of free glutamate in a damaged system you would have to take more than a healthy amount of aspirin. However, for mistakes when following a low free glutamate diet they can help.

Fran

PC, this is a link to a glutamate receptor researcher. Richard Hampson. He is in Canada. I wrote to him a while back about glutamate and AF, he pertained to be really interested and wrote back to me twice. He promised without prompting to get back to me if he came across anything. As of yet I have not heard a thing. Perhaps you as a Dr could speak to him on a level I cannot. Maybe he would feel better speaking to another Dr.

Just a long shot

Fran

http://www.utoronto.ca/grdpharm/hampson.htm

Hi PC. Great research and it's all starting to make some kind of sense (kinda). At least it gives us another path to follow. I would like to know if you could answer some questions regarding the supplements you mentioned in your post as well as some of the other posts. First, you stated in your post of 3/30 "this connection leads to a very easily designed supplemental regime that might possibly eliminate VMAF." This statement would certainly arouse the curiosity of any VMAFer, like myself. I might have missed something, but in reading the entire post, I didn't see any "designed supplemental regime." There is a lot of information regarding GABA, B6, Mg etc. but for someone like me with no medical background and limited experiences with supplements other than people saying "Take this. It's good for you," the task of designing a supplemental regime could be daunting and usually winds up being more of a "hit and miss." It would be helpful to know the dosages of the supplements in question, the timing of taking these doses (before meals, with meals, after meals, before bed, upon rising, etc.)

What started me questioning myself was reading the other posts on this subject. On your post to Jim of 4/1 you said "Take larger doses of B6." That got me thinking how much is larger? Then you told him, "Take your B vits with a protein meal." That's the first time I have specifically heard of that. Then you told him "Don't compromise all this by taking them with a competing substance, eg., Mg with fiber or milk." By this time I already have more than a few questions. On your post to Mike on 4/2 you advised him to "Be careful with Zn....." But on your previous post to Jim you advised him to "Don't lower your guard and forget Mg, Zn, hydration....." So by now I figure I better get the specifics of this whole regime. I mean, supplements are expensive enough, at least

here in Canada. Some of the better ones have to be imported from the US and that drives up the price also. So I want to be sure that I'm not wasting my money on supplements that aren't going to be absorbed or that are taken with the wrong kinds of foods making them inactive. On top of that, It would be prudent to ensure supplements are being properly absorbed in the right fashion so that one can honestly say "this is what worked for me," or "I tried that and it didn't work for me." I mean, THINKING you are doing the right thing doesn't matter.

First, perhaps you might be able to shed a little light on the following supplements mentioned in the posts. Perhaps there are others that would benefit from this info:

I could only find a B6 supplement that reads (pyridoxine HCL/pyridoxal 5 phosphate). Any observations/suggestions?

Re: COQ10 - Is water soluable best or the ones that need oil taken with them?

Re: GABA - Anything to look out for? I have to order it from the States.

So getting back to the "easily designed supplemental regime," What exactly would that regime be?

* Kinds of supplements (Names of brands if possible)
* Dosages
* Proper time to take them
* Proper foods (if any) to take them with.
* What supplements should not be taken with what other supplements (if any)

I realize that everyone must create their own regime to fit their particular situation as each VMAFer is different. But at least having some kind of guideline to start from would be helpful. And in the very least, knowing the proper kinds of supplements and the proper ways to take them would be very helpful and, I'm certain, enlightening to many. I'm certain that there are others like me, who find all the information encouraging but don't really know how to put it all together so that it makes sense. So we need some kind of a "bottom line" suggestion to start with. Any help from you or any other of the experienced posters would be gratefully appreciated. Thanks

Joe

Joe,

I won't go into a great deal of detail, because there is so much that I don't know but can only surmise.

First of all there is no panacea. But if you are a typical VMAFer here's what I would try. If you don't see an improvement in your HR within a week, then chances are you have no polymorphism for the P5P binding site.

Take at least 200 mg of P5P (pyridoxal 5 phosphate=the active form of Vit B6) in 50 mg tabs qid with a meal or something with protein (stimulates gastric acid secretion). Break it up with your teeth (fluid assistance helps).

At the same time I take 200 mg of GABA bid (you might see how the B6 works before you add this).

It is recommended that Vit C (as well as B6) be taken with GABA. I take 1 gm time release Vit C bid.

Vit B2 (riboflavin) is used to make P5P and niacin (Vit B3) and pantothenic acid (Vit B5) are important as well. So be sure to take a B complex.

RDA for Zn is 15 mg and at present I don't take more.

More importantly you should be taking lots of Mg. I take 122 mg Mg (as aspartate - helps in GABA synthesis; 1230 mg aspartate in Maginex-recommmended by Dr. Mannsman) bid and about 150 mg Mg (as lactate) and 200 mg Mg in ww and 300 mg Mg as citrate, orotate, and tartrate. Sometimes I drop the lactate form and use glycinate. Burton Silver, the founder of Inracellular Diagnostics, once told me that Mg absorption can occur via multiple amino acid and other pathways. You can easily saturate one by limiting yourself to a single supplement. I've been able to work up to this level over many weeks.

I think it is worth repeating that the synthesis of taurine and the elimination of homocysteine (bad marker for cardiovascular disease) require P5P. Folate also helps get rid of homocysteine.

As far as all the other supplements go I'm not an expert. Vits E,C,A are critical and CoQ10 would have to be up there too. Erling swear by it. But, like Mike, I'm trying to slim down on the supplements (although you'd never guess by the above list). Also arginine and ornithine (present in a balanced protein diet) are good for increasing GABA levels.

And lastly don't forget to keep hydrated.

And be patient but persistent, unless you see no improvement at all after a week or two.

Since taking larger doses of B6 my PACs have diminished dramatically. However, I have many dropped beats. These latter are not triggers of AF. I've been on GABA for a little over 24 hours and it eliminated over 70% of these night-time dropped beats. Its effect during the day has been even more dramatic. But it's too early to tell. Rest assured that you will all know when my next episode rears its ugly head.

Sorry about not answering all your questions, but I have many more than you.

PC

PC -

I've not had an AF episode since my PVA in late October (use to have them every week) but have been left with a very high number of ectopics (PACs and PVCs)...extremely disconcerting. My Dr. at the Mayo feels many are a result of the vagal tone. I have been reading with interest your comments, as well as many others, regarding research and suggestions. Could you please put this in plain English for dummies...there is so much to consider. I am hoping what is designed to help AF may also help my ectopics.

Am I correct that it is suggested to take:

At least 200 mg of P5P in 50mg tabs gid (?) with a meal or something with protein (such as?).
200 mg of GABA bid (?)...do I just ask for GABA or are they various forms, types, etc.?
Vitamin C.
Vitamin B2, Niacin and Pantothenic Acid...are they procured separately or can just one pill contain all?
Zn 15mg
Mg - am really confused as to the type of quantity.

B6 - how much?

Do you have any suggestions to as brands for the above. We have several great health food/nutrition stores so I would expect there will be many options.

I realize you must have been asked these questions repeatedly so I hope you'll bear with my very novice understanding of these supplements. But like the rest of us I'm looking for some answers and taking more heart rhythm medication, blood thinners, etc., is not the answer I seek.

Thanks for any help or suggestions you can provide.

Wade

Wade,

If you are really serious about controlling your vagal tone, I'd suggest getting a Polar S810 heart monitor. It comes with a chest transmitter and will give you beat to beat feedback on heart rate and heart rate variability. It can beat record up to 30,000 consecutive beats and you can download it to your computer. In my opinion it is much better than a Holter monitor in just about every way. Its only drawback is that it cannot differentiate between a PVC and a PAC. With it any improvement will be more apparent and objective, as opposed to some subjective impression. It will also motivate you and you will learn more about your own triggers and response to behavior and nutritional changes.

bid = twice a day
tid = thrice a day
qid = four times a day

GABA comes in several forms. The only one I would avoid is the one combined with alpha ketoglutarate. You may have difficulty finding this at your local nutrition store. I got mine at www.healthrecovery.com and its called Bio-GABA 100 mg per tab. According to Fran, some can react adversely to GABA, so start small. Just follow the directions about when to take (30 min before a meal with B6 and C).

P5P is the active form of Vitamin B6 (pyridoxine). Some people seem to have trouble making it (perhaps because it is required for its own synthesis). B6 absorption is compromised with pharmacologic doses of Vitamin C (no B6 2H before or after Vit C)

Vit B complex is widely available and contains all those I listed. Since the nutrition industry is not regulated, don't give up if you don't see results. Try another brand.

I take a multi mineral pill (tid) that contains mixed Mg chelates as well as Zn. I supplement with waller water (use the search function to learn more about this) which gives me about 150 mg Mg per day. I supplement this with Maginex tid and Mg SR (slow release) - see second hyperlink below.

You're going to have to educate yourself on all this. I suggest, as far as Mg supplementation is concerned, that you start with Dr. Mansmann excellent website at
https://secure.salu.net/cgi-perl/get.cgi?pub=50136&ext=doc
For the other supplements
https://secure.salu.net/cgi-perl/get.cgi?pub=50460&ext=doc

He recommends much more than 15 mg Zn. This may be a good idea, since Zn may be better than Mg as a cofactor for glutamate decarboxylase, at least in the brain.

Read as much as you can and many of your questions will be answered.

Don't be too obsessive-compulsive about things, i.e., what kind of protein, etc. I certainly don't have the answers.

This regimen seems to be working for me, but it may not last. Furthermore, it may not work at all for many.

PC

PC -

Thank you for your thoughts and insight. I will indeed review the reading material you suggested and research as much as possible as I go along. I realize what is one man (or woman's) honey is another man's vinegar. I will experiment and hopefully find a regiment that works for me.

Thanks again for your help!

Wade

Thanks, PC, for all the great info. I know the journey to "chronic NSR" will be longer than anyone would hope for. But I also realize that it took me 53 years to get to this point so with patience and the help of all the great people on this forum it will hopefully make the journey a tad shorter.....thanks again.

Joe

Good morning PC,

Just a quick insert here. I found Hyland's Homeopathic Mag. Phos. 6x at the naturopath, but one can get over the net. They are small pills that dissolve instantly in my mouth. The only downfall is they are in a base of lactose. There are 500 1-gr. pills for about $10, but cheaper on the net. It's hard to believe they are 1 gram, as they are so small. They are made by P & S Laboratories in Los Angeles. Have you ever used this?

Richard

Richard,

Good morning to you too.

Is this a B6 or Mg preparation?

PC

It's a Mg. prep, and I put under my tongue, even though it doesn't say sublingual, and it dissolves really fast. I'm going to check for B-6.

Richard

Richard

Just quickly I was given calc phos by the homeopath. The way homeopathy works is by giving very small, negligible amounts, of what is your problem. She thought that I was high in calcium. If it is not the problem then nothing will happen, if it does work it will irritate and for an unknown reason put you back on track. I hummed and hawed about it, then took it about 4 weeks later. I have to say I don't know if it has done anything. But if you take homeopathic strengths of Mg Phos it will not do anything as the amounts in it are negligible. Mine was in lactose sugar too, to be sucked. I have two more doses to take. I don't know yet.

Fran

Hi Richard

I realise it is a Mg preparation. The point I was trying to make is that it is in homeopathic quantities. Too little to make a change. In homeopathy they give you a bit of what irritates, not what you need, and for some unknown reason it stimulates the body to get better. Like cures like. So if calcium is the problem (eg too much) you take calcium and this stimulates mg to kick in - for some strange reason. I am supposed to take 2 tablets every six weeks - I don't know if I will take more. I don't understand the weight thing as my Calc phos is 30mg. So that is 60 mg.

From my limited understanding of homeopathy if you take Mg Phos this will stimulate the calcium to work. Just what we don't want. I may be wrong but this is the way my homeopath led me to believe it works.

Fran

Hello Fran,

Thank you for the heads up on that. It's a little confusing to me, as well. I'll ask the naturopath on Thurs. what it all means and let you know. I also want you and everyone else here to know, that I'm going to have every test, I can possibly have. I may look like a "junkie", with needle marks everywhere, but I want to know exactly what is going on in my body. I'll post all my results, as the tests are done. The first one I want is an amino acid panel. Thanks again, Fran. Just to let you know again, I have great admiration for you!!!!!

Richard

PC,

For myself and all the other AMAF'ers here I want to thank you for your concern for our condition and for including pertinent info for us too.

Obviously I understand your primary interest in VMAF, but just wanted to let you know there are AMAF'ers on this journey with you and we appreciate your keeping us in mind.

Thanks again from one who doesn't post much but who tries to follow along.

Rick S. AMAF,53

PC and anyone else following this thread,

Found this. Don't understand it wholly, except that fluoride may act as a GABA inhibitor. It has an option to email so I think copyright is covered. If you think it interesting perhaps visit this site where there is a page of GABA links and research at:

http://64.177.90.157/autism/html/gaba.html

Interestingly GABA inhibits thyroid hormone secretion.

Below from
http://www.ncbi.nlm.nih.gov/entrez/utils/fref.fcgi?http://linkinghub.elsevier.com/retrieve/pii/0968089696001459

Mechanism-based inactivation of -aminobutyric acid aminotransferase by 3-amino-4-fluorobutanoic acid

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Abstract
The mechanism of inactivation of the pyridoxal 5'-phosphate (PLP)-dependent enzyme -aminobutyric acid (GABA) aminotransferase by 3-amino-4-fluorobutanoic acid (2) has been investigated. As in the case of the homologue, 4-amino-5-fluoropentanoic acid (1), 2 equiv of radiolabeled inactivator become covalently attached to the enzyme, and no transamination, as determined by the lack of conversion of [1-14C] -ketoglutarate into [1-13C] glutamate during inactivation, was observed. In the case of 1, the conclusion was that inactivation was completely the result of modification of the coenzyme and that there was no metabolic turnover; every enzyme molecule catalysed the conversion of one molecule of inactivator to the activated species, which inactivated the enzyme by an enamine mechanism. With 2, however, 6.7±0.7 equiv of fluoride ions were released during inactivation, and it took 7.6±0.7 inactivator molecules to inactivate each enzyme dimer. Since no transamination was occurring, another metabolic event besides inactivation must result from the PLP form of the enzyme. Inactivation of GABA amino-transferase with [1,2-14C]-2 produced [14C] acetoacetic acid (about 5.5 equiv) as the metabolite. The 1.93±0.25 equiv of radioactivity covalently bound to the enzyme after inactivation with [1,2-14C]-2 and gel filtration were completely released by base treatment. HPLC analysis showed that three radioactive compounds, identified as 2, the product of reaction of PLP with acetone (3), and the product of reaction of PLP with acetoacetate (4), were detected. The release of 3 and 4 and the prevention of release of radioactivity by treatment with sodium borohydride are

consistent with the formation of covalent intermediates that have -carbonyl-like character, such as 6 and/or 7 (Scheme 2). Inactivation of [3H] PLP-reconstituted GABA aminotransferase with 2 followed by gel filtration then base denaturation released all of the radioactivity as a mixture of PLP, 3, and 4. Inactivation with [1,2-14C]-2 resulted in the release of 1.37 equiv of 14CO2, which was shown to be the result of decarboxylation of the acetoacetate/4 after release from the enzyme. These results are not consistent with a Michael addition mechanism (Scheme 3), but are consistent with inactivation by an enamine mechanism; release of the enamine five out of seven turnovers accounts for the formation of acetoacetate as the metabolite. To account for the detection of PLP and 2 after denaturation, it is suggested that a nonproductive formation of the Schiff base of PLP with 2 occurs in the second subunit of the enzyme; this complex is released and hydrolysed to PLP and 2 upon base denaturation.

Graphical Abstract
3-Amino-4-fluorobutanoic acid inactivates -aminobutyric acid (GABA) aminotransferase by an enamine mechanism, but five out of every seven turnovers it releases the enamine, producing acetoacetic acid.

Fran

Fellow fibbers,

Many/most of my GLU/GABA posts have touted this mechanism for VMAFers.

However, GABA is tremendously important in moderating/inhibiting the "monoaminergic systems" (norepinephrine, serotonin and dopamine) stimulated by stress and anxiety. Please see

http://www.nencki.gov.pl/pdf/an/an6034.pdf (just read the Discussion on pp 340-341)

This study was done on rats but to a certain extent that's what we've become!

In the absence of GABA the negative consequences (?AMAF) of these emotions are enhanced.

PC

This really is a most enlightening site for understanding the effects of GABA, glutamate and different disease states. About hypo-hyperthyroidism. I will eat my hat if this does not underlie all the causes of AF.

http://64.177.90.157/autism/html/glutamate.html

From PUBMED

Adult-onset hypothyroidism and the cerebral metabolism of (1,2-13C2) acetate as detected by 13C nuclear magnetic resonance.

Chapa F, Kunnecke B, Calvo R, Escobar del Rey F, Morreale de Escobar G, Cerdan S.

Instituto de Investigaciones Biomedicas, Universidad Autonoma de Madrid, Spain.

The effects of adult-onset hypothyroidism on the metabolic compartmentation of the cerebral

tricarboxylic acid cycle and the gamma-aminobutyric acid (GABA) shunt have been investigated by 13C nuclear magnetic resonance spectroscopy. Rats thyroidectomized as adults and age-matched controls were infused in the right jugular vein with unlabeled or (1,2-13C2) acetate solutions for 60 min. At the end of the infusion, the brains were frozen in situ and perchloric acid extracts were prepared and analyzed by 13C nuclear magnetic resonance and reverse-phase HPLC. Thyroidectomized animals showed a decrease in the incorporation of 13C from (1,2-13C2) acetate in cerebral metabolites and an increase in the concentrations of unlabeled glutamate and GABA. Computer-assisted interpretation of the 13C multiplets observed for the carbons of glutamate, glutamine, and GABA indicated that adult-onset hypothyroidism produced 1) a decrease in the contribution of infused (1,2-13C2) acetate to the glial tricarboxylic acid cycle; 2) an increase in the contribution of unlabeled acetyl-CoA to the neuronal tricarboxylic acid cycle; and 3) impairments in the exchange of glutamate, glutamine, and GABA between the neuronal and glial compartments. Despite the fact that the adult brain has often been considered metabolically unresponsive to thyroid hormone status, present results show metabolic alterations in the neuronal and glial compartments that are reversible with substitution therapy.

Parry-Billings M, Dimitriadis GD, Leighton B, Bond J, Bevan SJ, Opara E, Newsholme EA.

Cellular Nutrition Research Group, University of Oxford, U.K.

1. The effects of hyperthyroidism and hypothyroidism on the concentrations of glutamine and other amino acids in the muscle and plasma and on the rates of glutamine and alanine release from incubated isolated stripped soleus muscle of the rat were investigated. 2. Hyperthyroidism decreased the concentration of glutamine in soleus muscle but was without effect on that in the gastrocnemius muscle or in the plasma. Hyperthyroidism also increased markedly the rate of release of glutamine from the incubated soleus muscle. 3. Hypothyroidism decreased the concentrations of glutamine in the gastrocnemius muscle and plasma but was without effect on that in soleus muscle. Hypothyroidism also decreased markedly the rate of glutamine release from the incubated soleus muscle. 4. Thyroid status was found to have marked effects on the rate of glutamine release by skeletal muscle per se, and may be important in the control of this process in both physiological and pathological conditions.

and more. I think a low free glutamate diet would work wonders for all.

Effect of experimental changes in thyroid function on oxidative metabolism and glutamate dehydrogenase activity in the limbic system of the rat]

[Article in Spanish]

Fernandez-Pastor JM, Morell M, Menendez-Patterson A, Escobar-Bueno MC.

The oxidative metabolism and GDH activity has been studied in the following regions of the brain: frontal cortex, as tissue control, adenohypophysis, hypothalamus and limbic system in adult male rats subjected to alterations of the thyroid function due to excess (by hyperthyroidism with L-thyroxine and thyrotoxicosis with Tri-iodothyronine) or defect (chronic hypothyroidism by thyroidectomy, 131-I treatment and low iodine diet). A different influence of the H.T. was observed in these animals according to the areas studied and the experimental situation induced. All this seems to indicate an oxidative metabolic pattern peculiar to each area of the brain following H.T. administration. On the other hand, the decrease of the QO2 in chronic hypothyroidism in the majority of the areas studied is remarkable. In GDH results activity increased or decreased depending on the absence or presence of thyroid hormones.

Fran

Another tidbit of info. on amino acids.

http://www.ionsource.com/links/AAlinks.htm

Also, see:

www.orion1.paisley.ac.uk/Courses/StFunMac/glossary/industrial.html

This one states, that high levels of glutamate in the blood are converted to a-amino butyrate (AABA), which is similar to GABA (a nerve transmitter), so AABA disrupts nerve transmissions.

Fran,

Take note that glutamate is in our shampoos, detergent, etc.,

PC,

Still a little confused on just how to eliminate extra glutamate. Somewhere I read that l-cysteine synthesizes appropriate amounts of excessive glutamate, therefore lowering glu. By adding GABA and p5p, I don't see how this will eliminate excessive glu. that might be making AABA. Maybe if we avoid GLU like a plague, then it will eventually even out. I do understand your p5p theory and the importance of b6, and that will help with the enzymatic process, but what are your thoughts on eliminating excessive levels of GLU. I hope I'm not missing something here, and making you have to repeat yourself. If so, just guide me to re-read. Thank you.

Richard

Richard,

Sorry to be a bit tardy in responding. The ugly head of AF reared itself again. It was a most unusual episode. I seem to be at risk when I'm at the movies. Most of the time a swallow or walking up the stairs and sitting down after eating something is enough to trigger an event, but this was atypical. Almost two hours into the movie my HR was pretty good thanks to the P5P. But for no apparent reason the PACs started and voila - AF. I think it has something to do with the dark.

Anyway, back to your question. Undoubtedly Fran's approach of complete avoidance of glutamate is the best. But eating is like sex, it's hard to avoid. Glutamate is degraded by several enzymatic routes, only one of which results in higher levels of GABA. Taking arginine and ornithine theoretically pushes this reaction in the direction of GABA.

I think I have some more reading to do.

PC

Richard

I would watch the L cyseteine. From the Blaylock article above it says -" A growing list of excitotoxins is being discovered, including several that are found naturally. For example, L-cysteine is a very powerful excitotoxin. Recently, it has been added to certain bread dough and is

sold in health food stores as a supplement. Homocysteine, a metabolic derivative, is also an excitotoxin."

I learned a while back that glutamate was in soap and shampoo. Also in toothpaste, etc. I have found a source of shampoo and soap bars, even deodorant bars made with bicarb that I don't seem to react to. They are from Lush. I have to get them every time I go to Edinburgh as I can't source them from home. So my bathroom cabinet is stocked. Also I use bicarb for brushing my teeth.

I honestly believe that avoidance of free glutamate is the only way to even it out. I suspect I could get away with a little now but don't want to start the cycle again.

PC

These free glutamate foods are addictive. You can find lots of references to free glutamate acting as a drug on the body. It changes not only the way your brain perceives taste, but on the way your brain makes you feel. The food companies learned this a long time ago. We go back for more and more. Like any addiction it is hard to break. From my own perspective it was well worth it. I am wondering if your unusual AF was the result of GABA. In MSG sensitive circles it is a no no and the article that Erling put in showed it to have powerful effects on the ANS and heart rate. Still don't understand the reasons why as in theory it should work. But theory and practice..... need I say more.

Fran
