

THE AFIB REPORT
Your Premier Information Resource for Lone Atrial Fibrillation
Publisher: Hans R. Larsen MSc ChE

VIRTUAL LAF CONFERENCE

Proceedings of Fourth Session
March 1 – March 31, 2003

SUBJECT: GABA, GLUTAMATE and AFIB

Time to introduce a new subject!

I recently received an e-mail from an afibber who has found GABA (gamma aminobutyric acid) helpful in reducing the intensity of afib episodes. He is 55 years old and has a family history of atrial fibrillation. I did a bit of sleuthing on GABA and found that Russian researchers recently reported that GABA has antiarrhythmic properties as does the drug piracetam, which enhances the effects of GABA (1,2).

Other researchers (also Russian) have found that the anticonvulsant sodium valproate (Depakene), which increases brain concentration of GABA, also has potent antiarrhythmic properties (3). Sodium valproate is a pretty nasty fellow from what I can gather, but maybe it has a cousin with fewer side-effects.

I believe GABA is available in health food stores. Has anybody tried it?

Is there something here that should be explored in greater detail?

1. Tiurenkov IN and Perfilova VN, Anti-arrhythmic properties of GABA and GABA-ergic system activators. Eksp Klin Farmakol, 2002 Jan-Feb; 65 (1): 77-80 [Article in Russian]
2. Samvelian VM, et al. The antiarrhythmic action of piracetam. Farmakol Toksikol 1990 Nov-Dec; 53 (6): 22-3 [Article in Russian]
3. Meerson FZ, et al. Prevention of arrhythmias and cardiac fibrillation in acute ischemia and reperfusion by using a factor causing GABA accumulation in the brain. Kardiologija 1987 May; 27(5): 87-9 [Article in Russian].

Hans

Ah. Something I feel I understand a bit more....

I had wondered about this a while back as Glutamic acid is an excitatory neurotransmitter and is balanced by the inhibitory neurotransmitter GABA, while Glutamine is primarily an energy source

and mediator of both GA and GABA activity.

However, as Glutamic acid is a precursor to GABA and glutathione with the assistance of Vitamin B6 (= ?growth hormone), and Glutamate is a known antagonist to me I have preferred to leave well alone. I don't trust myself to be able to balance such things. They say that glutamic acid, present in monosodium glutamate, combines with a pressor amine like tyramine, commonly found in certain foods, including aged cheese, pickled herring, etc. It is this combination that produces the migraine headaches and palpitations associated with the consumption of such foods. Sensitivity to monosodium glutamate indicates a need for supplemental pyridoxine (B6) and manganese.

So by taking B6 and manganese if ingesting a high free glutamate diet, should give a natural source of GABA (but manganese is not something to play around with). I have always maintained that stopping all forms of free glutamate stopped my AF. I am very sure that my balance of GABA was brought about by balancing my diet and making sure I was ingesting enough vitamins such as B6 and Mg (not manganese) to combat the known high levels of intracellular calcium caused by free glutamate. Perhaps GABA as a supplement would work too. I would be interested in anyone else who has gone this route.

At the height of my sleep problems I believed that a lack of GHB (gamma-hydroxybutyric acid) was at the root of all my problems. GHB is biologically synthesized from gamma-aminobutyric acid (GABA), a structurally similar amino acid that is also widespread in human metabolism and diet. GHB is also biologically converted back into GABA. I even went so far as to print off how to make it my kitchen. I never did do it though as I had to import the ingredients and was working on doing it all naturally. GHB is also known as the date rape drug and is highly illegal. I was working on getting my GP to prescribe a form of it as narcolepsy was down as one of my ailments at the time. And it is approved for sleep disturbances. I may seem to have taken your post step too far. But in my book it is all tied up and very, very key to AF.

http://www.qhi.co.uk/features/feat_003.asp

GHB was first synthesized in 1961 by Dr. H. Laborit, a French researcher. In the brain, the highest amounts are found in the hypothalamus and basal ganglia [Gallimberti 1989]. Dr Laborit found that GHB exhibited a range of effects beyond those expected from GABA (which is established as a basic inhibitory neurotransmitter). GHB has come to be used in Europe as a general anaesthetic, a treatment for insomnia (sleeplessness) and narcolepsy (a daytime sleeping disorder), an aid to childbirth (it enhances cervical dilation) [interestingly this has been a problem in all of my deliveries the cervix did not dilate], a treatment for alcoholism and alcohol withdrawal syndrome, an anti-anxiety and anti-stress agent, and for many other uses. GHB is currently available by prescription in the US through compounding pharmacies. It has no formal drug status with the FDA (although 15 INDs are pending).

Fran

I don't know if anyone can see the AF connection with GABA. So I will try again.

<http://www.lef.org/magazine/mag99/sep99-report3.html>

The action of the heart is under considerable control of the nervous system, and the pathways involved in the neural control of cardiovascular function happen to rely on glutamate and GABA. If the brain has a faulty glutamine / glutamate / GABA metabolism, we can expect the development of cardiovascular dysfunction as well. In addition, glutamine serves as a substrate for the synthesis of a special type of beta-endorphin, glycyl-l-glutamine. This dipeptide appears to be

important for the regulation of blood pressure and prevention of cardiorespiratory depression. Glycyl-L-glutamine is also important for the immune response, since it enhances the activity of the natural killer (NK) cells.

- If any one of you has noticed MSG to be a trigger for AF, then it is more than likely that your body is not converting glutamic acid to GABA.

<http://www.cell-research.com/20004/204-MY.HTM>

This can mean that you are low on B6, in some people the enzyme glutamic acid decarboxylase is missing, or it is wrongly being attacked by the immune system. This has been shown to be happening in diabetes.

-(I still think of AF as a sort of opposite of diabetes). Like taurine, GABA has a "downer" effect to counteract glutamate's "upper" effect. Remember free glutamate with out calming GABA will literally stimulate a cell to death, if not to death it will excite it so that it fires and fires (sound like AF to you?). The reason for this is because it opens and keeps open the calcium channels, so that intra cellular Mg is too low. Extra Mg may help but it will not put it in the cell if the calcium channel remains open.

And for those of us finding great success with high protein diets look at this, <http://www2.uic.edu/~ktao1/KETOFINAL2.htm>

"The synaptosomal content of GABA is increased and maintained at a higher level by levels of ketone bodies. This phenomenon may contribute to the beneficial effect of the ketogenic diet."

And from the <http://www.msgmyth.com> do an on site search under GABA

"I repeatedly find that GABA, an inhibitory neurotransmitter which is the end product of glutamate, is found in large amounts in fresh tomatoes. Probably because glutamate, in the presence of vitamins B6 and C converts to GABA. In naturally occurring foods high in free glutamate with these vitamins intact, GABA should also be present. Also, these vitamins help the body make GABA from glutamate. Like taurine, GABA has a "downer" effect to counteract glutamate's "upper" effect. Anyone can tell you that vitamins stay more intact in unprocessed foods. Probably by destroying vitamins, processing has an indirect effect on our ability to deal with glutamate, by reducing the amount of GABA present, or our ability to turn glutamate into GABA. Processing is very hard on the B and C vitamins which we use to convert amino acids like glutamate.

As for dealing with the excess glutamate still present - Vitamin B6 is used by the body to turn MSG into a substance called GABA which also has the opposite effect of MSG. (GABA by itself though, is another story... it is addictive, and spurs the body to increase its output of growth hormones) - [there is a down side to supplementing it].

Taking the amino acid taurine and vitamin B6 together helps some people more than either by itself, as Tom Fernstrom reported on the NoMsg site. Don't overdose on B6 - the RDA is 2 mg. It's best to eat good sources of B6 instead of taking vitamins but if you do get an MSG reaction, be aware that the chemical structure of folic acid by nature contains a string of glutamates, so it might be best to take taurine and vitamin B6 only and avoid B-complex vitamins containing folic acid.

Carol H. made an astute comment last month stating that: "Those of us who get extremely anxious, and uptight, and feel pain are probably not very, very good at processing MSG and turning it into GABA...."

Office of the Hearing Clerk (1900)
Environmental Protection Agency (EPA)
1200 Pennsylvania Ave., NW.

Washington, DC 20460

Subject: "L-Glutamic Acid and Gamma Amino Butyric Acid; Exemptions from the Requirement of a Tolerance." Final Rule.
Docket Control Number OPP-301136

Objection: This is an objection to granting "L-Glutamic Acid and Gamma Amino Butyric Acid" an exemption from the Requirement of a tolerance.

Reason for Objection: Both of these chemicals are known to have a huge adverse impact on functioning of the human brain. L-Glutamic Acid and its chemical cousins including monosodium glutamate (MSG) are known excitatory neurotransmitters (excitotoxins). Gamma Amino Butyric Acid (GABA) is an inhibitory neurotransmitter. It is also a break down product of MSG.

Fran

Fran,

I'm intrigued by your statement that you consider "AF as sort of the opposite of diabetes". I know that in the previous Conference Room topic we discussed hypoglycemia and AF. Certainly some support for your view there.

I think you are very astute in so observing. I also think that AF is more of a problem in the thin (opposite of adult onset diabetes). VMAF is certainly more common in the physically fit and they, of course, would be on the thin side. What about a non-fit group of thin people v. overweight group?

Hyperthyroid afibbers also are thin and might benefit from a "downer" (?GABA). They would certainly fit the mould of being anxious and uptight with a low pain threshold. About 10% have AF.

I've noticed that I'm less likely to have an episode of AF during a cold. Others have also noted this. Look toward the end of this message (<http://www.medhelp.org/forums/neuro/messages/30220a.html>). This raises the issue of basal body temperature (hypothalamic thermoregulation) as a possible player in the onset of AF.

Could the connection between a thin habitus and VMAF be more than coincidental. Perhaps this is another question for Hans' questionnaire.

PC, MD v54

PC

Absolutely. I know Hans has done some sort of survey on the size and build of people with AF. I am sure that some of them are on the bigger size, in fact we probably mirror normal society. Of course long-term meds can change the way the body metabolises and many, myself included, did start putting on weight due to the long term effect of meds. However, when I stopped them I went back to what is my normal, a bit too much on the thin side (and I eat like a horse). I think it would be prudent to find out how long a partaker in any survey of this ilk had been on meds and what was their build before.

It may be a substrate of VMAFers 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. It then may be possible to demonstrate that based on symptoms in this category what the real problem is behind this form of AF. Of course GABA or lack of it comes out top in my book if I have understood what happened to me through diet.

For me about three days prior to catching a cold or a virus my Afib became worse. Once the virus takes hold AF was great (apart from sore throats, runny nose etc). And yes when I run a temperature it rarely goes to the highs that other people get too. So nobody gives me sympathy! I have also seen it mentioned by many Afibbers that they have strong immune systems. From the LEF link in my post above - "Glycyl-L-glutamine is also important for the immune response, since it enhances the activity of the natural killer (NK) cells" says it all. So whilst we rarely get ill, we make up for it with the inconvenience of AF and its other rarely looked at symptoms. All tied up there with glutamate and lack of GABA again.

I really hope this goes somewhere.... Like you with Magnesium, this is my pet theory. And of course the two are tied up due to the calcium channels and high glutamate

Fran

Hans,

How do you choose these wonderful topics? I've always wondered about GABA. But never pursued it. So many neurotransmitters, so little time.

Fran,

Another fabulous post. Did you spend the entire weekend in the library (or on Google)?

Sounds like the "date rape" med is just the ticket for me. Since my AF is definitely triggered by MSG and since I've had difficulty sleeping that has not been entirely "put to bed" by Mg, GHB may help. I'll write myself a prescription tomorrow (no need to have to convince someone I have narcolepsy) and let you know how it goes.

PC, MD v54

I had researched this before PC. So had a lot book-marked. It was the discovery of what glutamate can do to the nervous system, the science behind it and the effects of GABA and to an extent GHB that first led me on path to turning AF round. Of course I did not do it with taking GABA direct.

Its funny how you have gone straight to GHB (I keep wanting to write GBH- grievous bodily harm). That was my automatic want too as it gives you your circadian rhythm back, relieves anxiety and converts to GABA to boot. But I could not write my own prescriptions, GP would not do it until I had had sleep clinic, by which time I was better through diet and no meds. And at the time I was too scared to import the raw ingredients in case I was caught (there was wide coverage and scare-mongering of it on the UK news a while back where I learnt that I could make it with the aid of the internet!! - isn't the news a double edged sword).

Let me know how you get on with it. For me I will keep at this naturally. I really do believe that this is the missing link as far as others with continuing AF goes.

Fran

Looks like the "date rape" fear has removed GHB from the list of available pharmaceuticals on this side of the pond as well.

I couldn't find any place that still offers sodium oxybate (GHB). Interestingly, it not only is prescribed for narcolepsy but also fibromyalgia. But I kind of backed off when I read, "Sodium oxybate should not be given to patients with severe hypertension, bradycardia, conditions associated with defects of cardiac conduction, epilepsy, eclampsia, renal impairment, or alcohol abuse."

GABA also seems to be unavailable in the US.

Guess I'll have to be satisfied with the GH already onboard.

PC, MD v54

PC.

GABA is very available in the US. I just now went to iherb.com and saw GABA offered by many supplement makers.

Erling

PC

I know that some form of GHB was authorized by the FDA in the USA over a year ago but the guidelines for prescribing were very tight. I can't remember what the name they used was but I can look back and check it out later.

Interesting about the side effects as many people with those symptoms were taking it. There is a GHB group on the net somewhere, but I have not called in a while. It seems to fit in with Pfeiffer's side effects whilst supplementing with a large dose of GABA. I know that glutamate metabolism is so very key to my own AF, but GABA does promote growth hormones from the pituitary and MSG sensitive people do not supplement with it. I'm not sure of the real reason but will investigate further.

Fran

PC

Sodium Oxybate, Xyrem®) 3-9g Short duration of action, resulting anticonvulsant effects during daytime.

Was approved on July 17, 2002. Can be toxic at high doses and should be used under medical supervision.

Fran

There is a good anecdote in the book *The Healing Nutrients Within: Facts, Findings and New Research on Amino Acids* by Eric Braverman, MD, with Carl Pfeiffer, MD, PhD. (1987, Keats Publishing). It is in the chapter *Glutamic Acid, GABA, and Glutamine*:

"In studying the effects of amino acids in large doses, we were continuously impressed by their lack of toxicity. I found that by testing myself, I had no trouble tolerating 20 and 30 g a day of most amino acids. With GABA, the largest single dose that had been given to a human control I could find described anywhere was 3g. Overly confident, I took 10 g of GABA on an empty stomach. I should have been suspicious of GABA; after all, it smelled like a fungus or like a ginkgo tree. Another person called the odour a putrid sulfur smell.

About ten minutes after taking the GABA, I started to wheeze and my breath rate increased to 45 a minute. Five minutes later, my heart rate peaked at 140 and my blood pressure was 180/100. I was choking, fidgeting and could not sit still. I had a massive anxiety attack, thinking I was surely going to die. Hence, I called the Poison Control Center, which knew nothing of GABA, and they left me hanging on the line listening to music while I vomited into the waste basket. Over the next half hour, this anxiety attack let up, but I continued to be nauseous for the next two hours.

This dose of GABA also caused a constant flush sensation, like that of niacin, although my skin was not red. I had a tingling in my hands and over my entire body. This effect occurred even at the lesser dose of 3 g of GABA and is likely to be neurologic, unlike the effect of niacin, which is primarily vascular. This unusual tingling and flushing has been confirmed by several volunteers taking oral doses of 1 to 3 g of GABA.

Many younger scientists have been temporarily poisoned by their enthusiastic use of an initial large dose of an agent. I (Pfeiffer) recall my intrigue with early reports that a nasal spray formerly on the market would lower the body temperature of children. My colleagues and I found that this drug blocked oxidative phosphorylation in the test tube. The company sent out free samples of this drug in pediatric strength, which were minute -- only 2 ml of 0.05 percent. I took my temperature and swallowed the 2 ml dose. Within an hour I had pains and goose bumps all over my body. Despite an empty bladder I felt a constant need to urinate, and I slowly lost 1.59 degrees in body temperature. Within three hours the ordeal was over and I had learned that pediatric nose drops can be potent even in an adult. Such reactions teach us extreme caution as we continue to dream our impossible dreams -- to provide better therapy without drug side effects."

This important book has been out of print for some years, but according to amazon.com an update is now available -- the slightly revised title is: *The Healing Nutrients Within: Your Guide to the Best-Stocked Drugstore of All --The Human Body* (Eric R. Braverman, MD -- Dr. Pfeiffer passed away some years ago.) Amazon.com's description of the book:

"The two dozen amino acids present in the human body are now being shown to be among the most potent healing substances ever discovered. These constituents of protein are necessary to everyday life processes, but research and clinical work in the last two decades have revealed a vast range of therapeutic functions for amino acids, including phenylalanine's pain-relieving powers, tyrosine's energizing ability and addiction-fighting potential, methionine's role in Parkinson's disease treatment and as an anti-allergen, and homocysteine's emergence as a new and precise marker of heart disease risk. This update and revision of the landmark book on

amino acids covers the exciting discoveries of the last decade and shows how to use them in your personal health-management program."

Erling

Thanks for that Erling.

"In studying the effects of amino acids in large doses, we were continuously impressed by their lack of toxicity. I found that by testing myself, I had no trouble tolerating 20 and 30 g a day of most amino acids. With GABA, the largest single dose that had been given to a human control I could find described anywhere was 3g. Overly confident, I took 10 g of GABA on an empty stomach. I should have been suspicious of GABA; after all, it smelled like a fungus or like a ginkgo tree. "

This seems to contradict the 'known' inhibitory effects of GABA. Could it be a case of too much or too little creating the same symptoms? Carl Pfeiffer could almost have been describing an episode of AFib with his 10gms. For me a normal MSG reaction. Or could it be - Is enough is known about the way the body metabolises GABA direct? I mean we take glutamine or bound glutamate direct and our body turns it into the neurotransmitter free glutamate. With enough Vit B, C and manganese we then convert some of this into GABA to counter regulate the excitory effect of free glutamate. How then, can they be sure, when we take GABA direct our body does not metabolise it into something else, or tear it back down to free glutamate. These are all the questions that went through my mind when wondering whether to supplement with GABA. Of course Carl Pfeiffer probably did not need GABA as he had enough in his natural system and maybe when we take more than we need of something the body converts it back to its basic function.

I am fascinated to learn if anyone else has tried GABA and what the pros and cons, if any, were.

Fran (who is too scared to be a guinea pig)

Hi Hans,

I took GABA sometime in the past with no noticeable effects at all. I do not remember the dose, however I'm sure it was under 1gm. Seems not many things have an effect on me though. Wish I could add more.

Jim

Hi guys,

Really good post Fran, totally agree with you about the diabetes statement, I bet we've all got hypo tendencies even if we're not tuned into it

I've done my bit of reading like I need to in the conference room and the things that stands out the most for me is how GABA helps regulate blood pressure as most of our triggers promote changes in blood pressure (alcohol, caffeine, changes in position, hot baths etc) it could help .

There is a lot of links on the internet about supplementing in different ways and products to buy most of them saying it will help to bring down high blood pressure but what would it do to most vagal types with an already low blood pressure stabilize it or make it lower?

Just a thought but I'd be prepared to look into it and give it a try, its just deciding the best way to supplement any ideas?

Toni 29 alafer x

Hi Toni

The one thing that I haven't been able to do is bring up my BP. I have read all about kelp etc which is supposed to regulate both high and low BP. I could not supplement with kelp (as all the commercial types are roasted or simmered freeing glutamate, but ate it for a while freshly picked. But it made no difference to BP. I'll still pick a throng when on the shore at low tide and nibble at it for the mineral content, but no difference to BP...

If you try the GABA let us know how you get on? I would start, if it was me, with a low dose and do nothing else new so I could tell what was causing any effects.

All the best

Fran

Studies about GABA must be going on in the West too. I did not realise that midazolam is a form of GABA. And that the benzodiazepam group of drugs enhance GABA production. Could this all stem back to the fact that once upon a time for about two years I was on high doses of valium, and quit it cold turkey??

From <http://www.res.bham.ac.uk/publications/researchpubs/1988%20data/CARDIO.HTM>

Cardiac Autonomic Control (Dr. John Townend & Dr. Julian Vaile)

Mathew Farmer (BHF PhD student) has been studying the influence of GABA-ergic compounds on cardiac vagal function in humans. We are submitting a paper on the effect of IV midazolam (a GABA-mimetic agent) on vagal tone; work on flumazenil (GABA an antagonist) is underway.

The effect of GABA on cardiac vagal activity (Dr. Julian Vaile)

I have continued my collaboration with Matthew Farmer (PhD student in Physiology), examining the role of the neurotransmitter GABA on cardiac vagal control. We have completed a study of the effects of midazolam in patients awaiting cardiac catheterization, and have shown that benzodiazepine therapy, and thus GABA, are effective in inhibiting cardiac vagal tone. Further studies involving the benzodiazepine antagonist flumazenil are underway.

And

UNDERSTANDING GLUTAMATE EXCITOTOXICITY

Glutamate reuptake:

Only means of turning system off

Uses TWO reuptake pumps, one on neuron, the other on the astrocyte

Curiously, the astrocyte converts the glutamate back to glutamine and ships it to the neuron to be changed back to glutamate

The NMDA receptor: just ONE of three glutamate-activated ion channels known to be involved in excitotoxicity (AMPA and Kainate are the other 2)

A ligand-gated calcium channel

Like the GABA channel, has SEVERAL binding sites:

+ Mg⁺⁺ site INSIDE the channel, blocks Ca⁺⁺

+ PCP site INSIDE the channel - blocks Ca⁺⁺

+ Glycine site on receptor - excitatory

+ Zinc site on receptor - excitatory

+ Polyamine site on receptor - excitatory

Calcium, free radicals and excitotoxicity:

Over-excitation releases a flood of intracellular Calcium

Calcium does literally hundreds of things in the cell, many of which MIGHT be involved in excitotoxicity

Much interest has focused on the possibility that calcium ingress activates enzymes which produce free radicals, and these cause cell death.

Fran

I posted a question to the msgmyth site about why those with MSG intolerance do not supplement with GABA. This is the reply I got and later came a link. Posted for your information. Carol has the msgtruth site and used to work in the food industry.

<http://content.nejm.org/cgi/content/short/322/22/1555>

By Carol H on Wednesday, March 12, 2003 - 06:42 pm: Edit

Fran, GABA is an inhibitory neurotransmitter that has the opposite effect of MSG. It also works on the same receptors targeted by valium. GABA is the body's natural valium. However, GABA actually comes from glutamate. That is how the body defuses glutamate. It turns glutamate into GABA. (This is also the whole sick idea behind Auxigro - in the presence of vitamin C, glutamic acid is converted into GABA - the growth hormone for your veggies) Right now, though the folks who have Type I diabetes - most of them, anyway, have an immune system that attacks the very

enzyme that turns glutamate into GABA. This is no coincidence, I fear. A deficiency of GABA, means that our bodies are having trouble getting rid of MSG, a bad sign. Eating GABA, may not help the situation. Figuring out why the body is having trouble making GABA from the most abundant amino acid in the human body is probably more important. I wonder if the reason diabetics have this immune response is because the body is cranking out so much enzyme to convert excess glutamate (from eating too much MSG) into GABA that the body starts to rebel against the presence of so much GAD (glutamic acid decarboxylase). Perhaps this is why the body starts to ignore insulin too. What if, because the body can't get rid of the glutamate now, because it just destroyed the enzyme to do it, and since glutamate triggers the release of insulin, that the body starts to respond to the excess-glutamate-induced insulin like a person who has heard the fire alarm go off way to many times as a drill, that they refuse to respond to it anymore? It is interesting to note that diabetics often have concurrent cardiovascular troubles too, since insulin triggers the growth of the tissue inside the artery walls. I'll try to get more links on this.

Fran

Didn't quite know whether to post here or on the regular BB, especially since glutamate has been the subject of a recent thread. In fact it has made frequent appearances there, thanks to Fran. But I think that the intellectual firepower of the CR attendees make this the best forum for such a semi technical post. Furthermore, glutamate is kind of the opposite of GABA.

On 3/9/03 on the BB I posted an attempt to connect RSA (respiratory sinus arrhythmia) with VMAF. RSA is increased in the physically fit, as is VMAF. This connection appears to operate through cranial nerves IX and X (vagus) in the medulla oblongata (NTS, NA, DMNX). Please read that post to fully understand this one.

In a further attempt to understand why this occurs I started looking at neurotransmitters. I thought glutamate would be a good place to start. It is not only the most important neurotransmitter in the hypothalamus (1), but NMDA receptors mediate autonomic nervous system (ANS) activity in the hypothalamus, NTS, the NA and the DMNX (2). In that earlier post I argued that swallowing (deglutition), also mediated by NMDA receptors (2), triggers many VMAF episodes. This was meant to be representative of vagal input in general.

It would seem plausible to invoke an increase in the number of NMDA receptors in the NTS to mediate the increase in sensitivity to pulmonary stretch and baroreceptor afferents (sensory). This increased vagotonic activity is probably exerted through the NTS since 80% of vagal fibers are afferents (sensory) (4). The NA and the DMNX are the efferent (motor) arm of the PNS. The body frequently upregulates neurohormonal pathways by increasing the number of target receptors.

Furthermore, the hypothalamus, the Area Postrema (AP) and the NTS (all are circumventricular organs) do not have a blood brain barrier (3). Sympathetic neurons in the medulla (specifically the rostral ventrolateral medulla) receive tonic glutamatergic excitatory input from the hypothalamus (6). The AP interacts with vagal afferents and communicates with the NTS (5). This means that MSG and aspartame, which do not cross the blood brain barrier, have direct access to these increased NMDA receptors. This would explain the sensitivity of many VMAFers to these excitotoxins. Excess glutamate could provide all the ingredients for AF, namely shortening of the refractory period, increased dispersion of refractoriness, slowing of cardiac conduction (all vagal effects) and automaticity for PAC triggering (sympathetic effect).

In the cited example (3/9 post), the individual, who exhibited EKG documented bradycardia (frequently leading to AF) triggered by swallowing, also reported that this "swallowing triggered bradycardia" disappeared during a cold. The preoptic anterior hypothalamus controls

thermoregulation and may in some way block vagal afferents. I'm still trying to figure out how this might work. Also, the paraventricular nucleus of the hypothalamus is intimately involved in neuroendocrine regulation. The hypothalamus often intermediates between the cortex (upper motor neurons) and the brainstem (lower motor neurons) to integrate conscious activity. This suggests that glutamate may play a role in not only VMAF but also AMAF as well.

Note: The brainstem is composed of the midbrain, the pons and cerebellum, and the medulla (moving from top to bottom).

This may all seem like an idle exercise in mechanism hunting, but avoidance strategies can much more easily be discerned.

- 1) Excitotoxins - The Blood-Brain Barrier <http://www.nisbett.com/nutrition/excitotoxins03.htm>
- 2) Immunolocalization of NMDA receptor subunits 1 and 2a/b on neurons in the nucleus tractus solitarii and in the vagal motor nuclei of the rat
<http://www.physoc.org/Proceedings/Abstracts/501P/Dublin/cardioresp/S17>
- 3) Neural pathways from the immune system to the brain
<http://www.john-libbey-eurotext.fr/articles/ecn/8/2/221-3/>
- 4) The Polyvagal Theory <http://www.wam.umd.edu/~sporges/polyvag/polyvag1.htm>
- 5) The Polyvagal Theory: Phylogenetic Substrates Of A Social Nervous System by Stephen Porges, p. 139
- 6) Medullary And Supramedullary Mechanisms Regulating Sympathetic Vasomotor Tone
<http://www.neuro.gu.se/neurofys/Satellite2002/speakers/Dampney.pdf>
- 7) Brain Neurotransmitters
<http://www.benbest.com/science/anatmind/anatmd10.html#glutamate>

PC, MD v54

PC

Thanks for doing this. I could never hope to be able to put this across in such technical language, a language which is needed for people to take it as seriously as it deserves - where AF of both kinds could be helped. I feel bad about this but I am going to revert this academic topic back into the language I feel comfortable expressing in my usual emotive style.

You said that "Excess glutamate could provide all the ingredients for AF, namely shortening of the refractory period, increased dispersion of refractoriness, slowing of cardiac conduction (all vagal effects) and automaticity for PAC triggering (sympathetic effect)." Also, "This may all seem like an idle exercise in mechanism hunting, but avoidance strategies can much more easily be discerned".

This is what I discovered. 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 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.

I just want to stress though that eliminating everything that says MSG on its label is not enough. Enough is knowing what foods contain it naturally, what additives contain it and how the food or supplement you are taking has been made. As processing of any kind (including over cooking food in the kitchen) will free glutamate. That is why I shiver when I read of high protein diets with protein shakes. The very act of making protein into a powder releases the glutamate from its bound enzyme chain and you are ingesting free glutamate and making the situation cycle. The

same has to be said of many supplements and even medicines and injections!! (read the article I posted on the regular board about sources of free glutamate). The binders, fillers and coatings, carrying agents are full of free glutamate. I swear the reason I am AF free is because I am supplement free (remember that Mg citrate put me in AF after one tablet). IT does not take much free glutamate to cause a reaction, especially if a person is taking the supplements day in and day out. If only a pure source could be found without all the additives for shelf life, to stick it together, to disperse it in....

I have often wondered if there are NMDA receptors in the pulmonary veins. They are still to discover there total whereabouts. I wondered this because of the success rates of ablation. I knew it was not getting to the root of AF, but wondered could it be burning out the receptor which caused it. I wrote to an NMDA researcher who answered my first two emails and said he was very interested in this theory. He was going to check whether there was anyone looking into this or researching it - But sadly he never got back to me.

I would love to dare someone not on AF meds (which also contain free glutamate) to give up ALL processed foods, natural food sources high in free glutamate and supplements for a month and see how they fair. There are very few supplements or meds that people with MSG sensitivity can safely take. Read msgmyth site to see why.

Now I fear I will get bombed out for daring to think that supplements and meds because of their free glutamate content may actually further AF. After all Erling is AF free and takes some supplements. But for all those not taking free glutamate in diet, on a high protein diet and still supplementing with AF, it does make me wonder. I have spoken with two other Afibbers who have stopped AF through this method. I know Jerry does not like this line of thought as I put it forward before. He bombed it right out saying that free glutamate is perfectly safe for all but the odd highly sensitive person (what else is someone with AF). But if it works for me and others it shouldn't be knocked. It should not be thrown out and me made to feel like a freak of nature who is just highly sensitive. I had AF the same as everyone else. I don't believe I am the only one with this form. So it should only be thrown out on an individual basis after they have tried and tested it.

Fran (A VMAFer for 20 years before she discovered this. And would like to save others from the same ordeal.)

Fran,

I think your most recent post on the BB fits right in. I agree wholeheartedly on the hypoglycemia connection, as you well know.

I believe that the sequence of events in a VMAF episode goes something as follows:

- 1) High vagal tone situation, usually but not necessarily at night, since that is the peak of vagal tone in its diurnal variation. Vagal stimulation secondary to eating, GERD, hunger, etc.
- 2) An activity or physiologic state that elicits catecholamine secretion. Hypoglycemia would be a very prominent one. Others include dehydration, hot bath or alcohol (peripheral vasodilatation with drop in BP), also postprandial state (congestion of splanchnic bed for absorption of food with drop in BP), simply walking up stairs after a meal. Caffeine also stimulates catecholamine release. Incidentally the amount of caffeine in chocolate and the primary role of chocolate in this pre AF cascade is probably through reactive hypoglycemia.
- 3) A final triggering vagal maneuver (mediated by the baroreceptors) like bending over, lying down, sitting down, swallowing. Even something as simple as bending over after a sprint to catch your breath.

I think all VMAF is triggered by a vagal maneuver during high vagal tone. This is what differentiates VMAF from AMAF. The PACs (from #2 or from excitatory elements like MSG and aspartame) are potentiated by the vagal state (shortened refractory period, etc.) and finally eventuates in an episode.

Therefore, removal of any of the contributing elements should create a break in the cascade.

The hypoglycemia from PRH may well explain your continuing PACs. Your lack of VMAF due to vigilant avoidance of MSG suggests that MSG may play a large role in creating a vagotonic state.

I think that all those daily extended workouts by endurance athletes caused the body to slowly increase the number of receptor sites in nerves (NTS) receiving its signals from the baroreflex receptors to slow the HR after the workout. The pressure sensors became more sensitive. These proliferating receptors are NMDA in type and glutamate is the neurotransmitter. Perhaps your severely restricted glutamate intake caused these NMDA receptors to wither resulting in a less sensitive pressure setting.

The picture is quite complex and not as simple as I've indicated. There must be tremendous variation from individual to individual wrt the involved physiology. Perhaps a good provocative test for MSG sensitivity would be to ingest plenty of dried seaweed for dinner and see how many PACs appear during the subsequent evening.

I am most interested in your comment MSG and injections. Could you expand on that a bit.

PC, MD v54

<http://www.truthinlabeling.org/Mercury&MSGinVaccines.html>

"Vaccines

Many parents of autistic children believe that their children's autism was caused by mercury present in one or more of the vaccines given to their children. It has been suggested that the growing incidence of autism may, or may also, be related to the processed free glutamic acid (MSG) found in vaccines.

Most, if not all, live virus vaccines contain processed free glutamic acid (MSG). The Rotavirus vaccine, a live virus vaccine that has been withdrawn from the market, actually included a caution that the product should not be used on infants who were hypersensitive to monosodium glutamate. Sterile (dead virus) vaccines, including the current (2003) flu vaccine, may also contain some processed free glutamic acid (MSG).

It would seem that not only are both mercury and MSG suspects as causative factors in autism, they may be interactive. Most vaccines include thimerosal, a preservative that contains ethylmercury. Aschner et al. (Methylmercury alters glutamate transport in astrocytes. *Neurochem Int.* Aug-Sep, 2000; 37(2-3):199-206.) found that:

"In the absence of glutamate, neurons are unaffected by acute exposure to mercury, suggesting that neuronal dysfunction is secondary to disturbances in astrocytes (Brookes, 1992). Co-application of nontoxic concentrations of MeHg [methyl mercury] and glutamate leads to the typical appearance of neuronal lesions associated with excitotoxic stimulation (Matyja and Albrecht, 1993)."

Clearly thimerosal contains ethyl mercury, and Aschner et al. worked with methyl mercury.

However, we have been led to believe that the effects of mercury would be the same for both ethylmercury and methylmercury".

http://www.priorityonevitamins.com/pharmacy/articles_info.php?articles_id=16

"Glutamate can be found in anything protein-fortified, enzyme-modified, and fermented. It can appear where consumers least expect it such as in the new chicken pox vaccine. Most canned tuna packed in water contains free glutamate as hydrolyzed protein.

There has been an enormous amount of evidence that the ingestion of free glutamate can bring on serious health problems. It can extend far beyond the so-called "Chinese restaurant syndrome." The reactions usually involve different body systems, especially the brain. Many people are experiencing adverse reactions to free glutamate and do not know the cause. In sufficient quantities, free glutamate is toxic to everyone. To those who cannot metabolize it effectively, even smaller doses can act like a poison.

There is also the issue of whether the widespread promotion of MSG may contribute to the dramatic increase of Alzheimer's disease, ALS (Lou Gehrig's disease), and Parkinson's disease. The blood-brain barrier, once thought to protect the brain from the unregulated flow of MSG is damaged by conditions such as trauma to the head, stroke, diabetes, hypoglycemia (low blood sugar), and aging."

Is the reason that many of us react to free glutamate because of an underlying hypoglycemia? I don't know for sure for others, but my experience and the research certainly suggest that this is what has happened to me.

And is it glutamate that makes mercury so much worse for some people?

PC I think what you wrote is spot on. And yes it is very much more complex than that. 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. The bottom line is avoidance.

Fran

P.S. Based on the few mistakes I have made I would not dare try the seaweed test. I know I would end up in AF, not just PACs. PACs in my book are limited to PRH.

Fran,

Thanks so much for the information.

I have to agree with the role of glutamate in LAF. Glutamate as a neurotransmitter appears to be quite prominent in the ANS. For those that think I've abandoned Mg think again.

When glutamate or aspartate (aspartame in nutrasweet is metabolized to aspartate) attaches to the NMDA receptor, it triggers the flow of sodium (Na) and calcium (Ca) ions into the neuron, and an outflow of potassium (K), firing the neuron. ATP pumps are required to return the ions and restore the resting state. The Ca channel is blocked by magnesium. This helps maintain membrane potentials near resting value. If the repolarized or resting state cannot be maintained, e.g., hypoglycemia, defective pump (as in Mg deficiency), then the neuron fires and the channels open. This pump failure gradually allows excessive calcium/sodium build up inside the neuron, which is eventually lethal. Furthermore, ATP pumps are required not only to return the ions but also to remove the glutamate and return it to the neuron (neuronal reuptake). Glutamate is then

converted into glutamine, another process that requires ATP. That is a total of three separate ATP and Mg requiring steps.

I think a very good way to cut down on the number of VMAF episodes is to avoid "autonomic oscillations". For example, don't bend over after running around, especially in the evening. Enjoy your dinner. Eat early, slowly, small portions and don't leave the table so quickly. Relax afterwards.

If you're on your feet all day, be sure to hydrate. Standing causes movement of fluid from the vascular space to the extravascular space with a slight drop in BP. This causes a reflex increase in catecholamines, which heighten the susceptibility to a vagal maneuver triggering an episode. Hypoglycemia creates the same situation.

My personal belief is that VMAF (wish I knew more about AMAF) is triggered in an atmosphere of a high autonomic setting (I think VMAFers already have a high setting, not more neurotransmitter, just more receptors). The net difference between vagal and sympathetic tone is maintained as usual. However, the background activity for both is increased. Since the response time is different (sec for the SNS and msec for the PNS), any opposite autonomic actions quickly performed in short order can create the needed imbalance to trigger an episode. Mg deficiency would certainly aggravate this.

Figure out not only what your particular triggers are but also what the sequence of events is. This will help you identify your at risk situations, not just the actual triggers. A diary is indispensable for this.

PC, MD v54

<http://www.mcmaster.ca/inabis98/klip/muth0302/>

This might be of some interest. I'm still trying to digest this info. and read all of your links.

Richard

Do you think that Mg deficiency or hypoglycemia comes first (prior to onset of AF)? eg If for any reason (e.g. not enough ATP energy to maintain the resting potential) the surface membrane electrical charge of the cell drops to -65 millivolts, allowing the neuron to fire, the magnesium block is overcome, and the channel opens, allowing the sodium and calcium to flood the neuron.

Which would indicate that I was first hypoglycemic or Mg deficient before AF reared its ugly head. THEN this made me sensitive to free glutamate, which in turn led to chronic excitability and anxiety over the years with escalating mg, GABA etc deficiency. Not getting better until I stopped free glutamate.

Or could it be that free glutamate caused the reactive hypoglycemia first (as it is implicated in causing hypoglycemia and many other syndromes) which when sustained caused chronic AF and all the other deficiencies and symptoms.

I suppose this is like asking is it twelve eggs or a dozen eggs, but it does matter.

I am asking because you seem to be saying that the damage done by free glutamate can be undone by supplementing with Mg and a low glycemic diet. However we are all exposed to high

free glutamate from birth, even 'healthy' eaters. Even those who eat fresh food with the help of cereals, sauces, yogurts and skimmed milk etc). And what role does Mg deficiency play in all the healthy eaters who have never been subjected to Mg deficiency in their diets? For those who do not have a reactive hypoglycemia? Glutamate toxicity would mean that Mg was not being metabolised correctly, no matter how much they ingested. I can see evidence for this in some on this very board

If it were just glutamate toxicity that caused everything else, then even AMAFers could look to this and experiment with it as a cause too. But to experiment does mean complete avoidance.

Am I right in thinking that if glutamate is not removed from the neuron (hence excitability) then the body cannot make glutamine and hence GABA?

If this is the case I would like to surmise that my body now produces GABA and through adequate diet my body has rebalanced with no more AF and can sleep again. In hindsight it makes sense that I had no GABA. GABA is the body's valium (valium fits this receptor). I lived in a state of extreme anxiety (but don't believe it was just down to Mg deficiency).

Thanks again PC and HANS for allowing me to air my own views on AF, not necessarily to the detriment of the Mg theory. I know that Mg plays a huge part. But there are people who have plenty of Mg and still AF. The story has to be wider, or deeper. And I am sure it is glutamate toxicity that underlies it all.

Fran

Fran,

I'm sure glutamate toxicity is caused by more than just Mg deficiency. Many with Mg deficiency have no problem with MSG and many with MSG problems have plenty of Mg, as you have pointed out.

Etiology of hypoglycemia likewise must be quite complicated. We've already discussed PRH and one possible mechanism via Mg deficiency and its role in proper glucagon function. If correction of a demonstrated Mg deficiency does not result in improvement in glucose metabolism, then its contribution would have to be viewed as minimal to absent. In fact on balance I would have to say that Mg deficiency would have to be infrequently the problem in PRH. After all, Mg deficiency is more often associated with impaired glucose metabolism and hyperglycemia than with hypoglycemia.

Regarding glutamate and Mg deficiency, I think similarly, i.e., that Mg deficiency is only a small time player. Hypoglycemia on the other hand has been directly implicated in potentiating the danger of free glutamate. Glucose is more important than Mg in maintaining cellular homeostasis, especially in the brain. I have to plead ignorance on the mechanism through which glutamate causes hypoglycemia.

I'm continually touting the benefits of adequate Mg intake. This is mainly because it is a no brainer - so easy to do. Correcting the glutamate problem on the other hand is more elusive. Perhaps that is why it is so unappreciated. I certainly don't think Mg replacement is the panacea for free glutamate problems.

I've read most of what you've contributed on this BB about glutamate and have to defer to your wealth of knowledge on it. I can only agree wholeheartedly with you when you say that VMAF is wider than Mg deficiency. It may also be wider than glutamate sensitivity/intolerance. I'll have to look at glutamate/GABA physiology more closely.

PC, MD v54

That would be great PC. With your inside knowledge you would understand it all better than me and reach a far wider audience.

Yes it has to be wider than glutamate too. Many can take processed foods with no apparent problem. At least avoidance can stop it for me, but it is a real pain. The day I can go out for a meal again would really make me smile.

I really appreciate your interest in this subject as will the many it helps in the long run.

Fran

Fran,

Here's what I was able to dig up on the question of glutamate, GABA and Mg deficiency:

Glutamate (a major excitatory NT) is converted into GABA by glutamic acid decarboxylase (GAD) when in the presence of the co-factor pyridoxal phosphate. This is the rate limiting step.

<http://www.exocortex.org/neurosci/gaba-nt.html>

Pyridoxine (Vitamin B6) requires phosphorylation to become active, and this phosphate transfer reaction is magnesium dependent. A magnesium deficiency may cause a relative B-vitamin deficiency.

<http://www.mgwater.com/gaeffect.shtml>

Thus, Mg deficiency may result in less GABA and more glutamate.

Good website for Vit B6 information:

<http://www.anyvitamins.com/vitamin-b6-pyridoxine-info.htm>

In addition magnesium is also required for the production of melatonin.

<http://www.nutritionreviewservice.com.au/summary.PDF>

So there are many reasons for Mg deficiency to cause poor sleep pattern. I find that for me PACs, leg cramps and difficulty sleeping are almost always found together.

PC, MD v54

Fran,

To further underscore the importance of glutamate and Mg in the genesis of VMAF through pyridoxal phosphate, the following websites are quite informative:

<http://www.nutrition4health.org/NOHAnews/NNSp99B6.html>

<http://www.worldwidehealthcenter.net/article.php?article=115>

<http://www.mgwater.com/gaeffect.shtml>

Perhaps a trial of pyridoxal 5 phosphate or pyridoxal phosphate (v. straight pyridoxine = Vit B6) would be in order. B vits are water soluble and there isn't significant toxicity risk, at least at dosages less than 500 mg. I'm presently taking 50 mg, which is 2500% of the RDA. Never checked my homocysteine levels, but this regimen would be especially advisable if that happened to be elevated, especially if such an individual was already taking 400 mg folate. Jackie has talked about this a bit in past posts on the BB. I'm going to have to reevaluate my dosage, how I take it and when I take it. Gotta get a good source for p5p. Vit B6 is not only required as a cofactor for all decarboxylase reactions (not just the rate limiting glutamate to GABA one) but it also helps in the absorption of Mg.

This information combined with the fact that vagal control of baroreceptor and SA node activity is mediated via glutamate (as a neurotransmitter) acting on NDMA receptors may indicate the final common pathway for explaining VMAF wrt Mg and free glutamate.

PC, MD v54

It is so easy to see why Mg is such an important mineral.

Thanks for all the links. My reading list is getting longer (I have gotten behind in this lately due to 'life'.

Many years ago I was prescribed pyridoxine for premenstrual tension. Of course it probably had no phosphate in it. It worked wonders in the beginning then stopped working (makes me think about how the body becomes lazy and stops processing it from food if it is getting it from another source - sort of like morphine and endorphines, or the one closer to home valium versus GABA).

I tried a complex vit B tablet earlier this year and ended up being very anxious on it. So am a bit afraid to experiment again. I just wish I hadn't become so darn sensitive (but after 20 years on serious meds what can I expect). But as time goes by I have noticed I am able to slip a little bit of previous no -nos in. So maybe p5p is in order if I can find a good source.

Thanks again.

Fran

Fran,

It took me awhile to find it but the following website sells 100 capsules of Vit B6 as pyridoxal 5 phosphate 50 mg for \$15.

http://www.healthrecovery.com/PageMill_Product_Files/BioP5P.html

I plan to start experimenting immediately, first by going from 50 mg/d to 200 mg/d (pyridoxine). If that helps keep the PACs down, I'll try the P5P.

I also found that Vit B6 deficiency is also associated with nighttime leg cramps too. Additionally there's plenty of biochemical opportunities for it to contribute to hypoglycemia as well and it is a prime deficiency in alcoholics. And one last point, pyridoxal 5 phosphate is especially responsible for dreams. Hopefully I'll have a few tonight for the first time in a long time.

PC, MD v54

Also thanks to Erling's Rosedale article I found this article by Cordain on the effects of cereals on B6.

<http://www.dfhi.com/interviews/cordaingrain/cordaingrain.html>

Although table 4 suggests that most cereal grains except for oats are relatively good sources of vitamin B6, the bioavailability of B6 from cereal grains tends to be low, whereas bioavailability of B6 from animal products is generally quite high, approaching 100% [60]. Vitamin B6 exists in foods as three nonphosphorylated forms (pyridoxine, pyridoxal and pyridoxamine) and two phosphorylated forms of pyridoxal and pyridoxamine. An additional glycosylated adduct of pyridoxine, pyridoxine glucoside, occurs widely in cereal grains and has been shown to reduce the bioavailability of both nonphosphorylated and phosphorylated forms of vitamin B6 by 75–80% [60, 61]. The presence of pyridoxine glucoside in cereal grains has an overall effect of depressing the vitamin B6 nutritional status [62]. Data from Nepalese vegetarian lactating women has shown a low vitamin B6 status for both the mothers and their infants which was partially attributed to the high levels of pyridoxine glucosides found in their cereal-, legume- and plant-based diet [60]. B6 deficiencies appear to be quite common in populations utilizing cereals and pulses as staples [63, 64]. Low tissue levels of vitamin B6, like vitamin B12 are known to elevate plasma homocysteine levels and increase the risk for arterial vascular disease [43]. To date, plasma homocysteine levels have not been evaluated in cereal- and pulse-eating populations of the Indian subcontinent wherein there is a high mortality rate from CHD [36].

Fran

Vitamin B6 Catch 22

The problem with Vit B6 is that it has to be phosphorylated (to become pyridoxal 5 phosphate = P-5-P) before it can become active as a cofactor in any enzymatic reaction. However this phosphorylation reaction is mediated by pyridoxal kinase, which itself requires P-5-P and Mg. This is a catch 22 and similar to the problem in Mg deficiency (Mg is required for its own absorption). Furthermore, some of us (especially me) have become so preoccupied with replenishing Mg via WW and the like that we have probably become marginally deficient in P. My intracellular mineral analysis after 2 months of WW was at the very lower limit of normal. This may in part explain why some involved in the WW trial experienced initial success only to have it slowly erode subsequently. Although phosphorus deficiency from a regular diet is nearly impossible to achieve, antacids (read Mg or WW) can bind ingested P and cause such a deficiency.

The list of diseases associated with Vit B6 deficiency are strikingly similar to those associated with Mg deficiency.

Vit B6 Deficiency - PMS, asthma, headaches, depression, fibromyalgia, epilepsy, schizophrenia, pre-eclampsia, seizures, leg cramps, autism, hyperacusis (increased sensitivity to sound), osteoporosis, seborrheic dermatitis, attention deficit disorder, arthritis, peripheral vascular disease,....

Mg deficiency - everyone of the above + many others

Mg is involved in over 300 enzymatic reactions in the human body.

P-5-P (requires Mg) is involved in over 100 enzymatic reactions in the human body.

Is it any wonder that when deficient, they both share many of the same symptoms and diseases?

<http://www.gutdoc.org/VitaminB6.htm>

http://home.caregroup.org/clinical/altmed/interactions/Nutrients/Vitamin_B6.htm

So it appears that perhaps VMAF is caused by an excess of glutamate over GABA and that perhaps adequate Vit B6 and P (both required for P-5-P) and Mg are all required to banish VMAF. For the above reasons P-5-P and Mg are particularly refractory to replenishing.

PC, MD v54

Hi PC,

Just a quick insert here about phosphorous. At the onset of my condition, I had flutter, which started about 2-1/2 yrs. ago. On 3 separate occasions, when I was in flutter, I had a Coke, which brought me back to SR within 30 minutes. My wife thought it was the caffeine, but we figured it out, to be the phosphoric acid in the Coke. We mentioned this to the EP, and she noticed I was on the low side of phosphorous, even though serum Mg. and Ca. were normal. Don't drink them anymore, though.

Richard

Richard,

Thanks for the input. I was just thinking about that very aspect of Coke over the past few days. I used to drink it quite regularly and this no doubt contributed to my low levels of Mg. With all this emphasis on Mg I think the shoe is on the other foot now.

Since Mg has a diurnal variation and is lowest at night, I drink all of my daily ww (300 mg Mg in a liter) starting immediately upon arising to exploit this diffusion gradient. I concentrate on P containing foods in the afternoon to minimize the Mg-P binding in the GI tract.

I also take almost 400 mg of elemental Mg as glycinate and 84 mg of slow release Mg as aspartate in the AM along with Vit B complex containing 200 mg of B6. The latter not only helps Mg absorption, but helps Mg biochemistry/physiology. It's absorbed in the proximal small bowel and the more gastric acid the better the absorption. So I add this all to a protein shake, since protein stimulates gastric acid secretion. Fran has expressed reservations about protein mixes, but this has not caused me any problems over the past 4 weeks while taking it. My diet has traditionally been typical American - way too many carbs in the AM. I hope this is an improvement. At least I've no more seborrheic dermatitis.

PC, MD v54

Hi PC,

Well I spoke too soon. I awoke with AF this morn., but took a phosphorous mixture (250mg) that brought me back to SR, with the HR still a little fast, within 30 minutes. Thought I'd try that first, just to see what the results would be. I ate an apple about 9pm last night, so am wondering if that's what did it. I also ate a ribeye for dinner that wasn't as tender, so maybe it didn't digest as easily. Anyway, to my point.

I have been reading here, and referring to my book mentioned on the BB, and I wanted to quote something.

"Given a rich supply of essential amino acids (EAA) and the critical co-factors alpha-ketoglutarate and P-5-P, the liver can easily maintain demands for non-essential counterparts." pg.86

The addition of these two components appears to aid the efficiency of epithelial cell utilization of glutamine. pg.219

Another site:

The alpha-ketoglutarate dehydrogenase complex (KGDHC) is an important mitochondrial constituent, and deficiency of KGDHC is associated with a number of neurological disorders. KGDHC is composed of three proteins, each encoded on a different and well-characterized gene. The sequences of the human proteins are known. The organization of the proteins into a large, ordered multienzyme complex (a "metabolon") has been well studied in prokaryotic and eukaryotic species. KGDHC catalyzes a critical step in the Krebs tricarboxylic acid cycle, which is also a step in the metabolism of the potentially excitotoxic neurotransmitter glutamate. A number of metabolites modify the activity of KGDHC, including inactivation by 4-hydroxynonenal and other reactive oxygen species (ROS). In human brain, the activity of KGDHC is lower than that of any other enzyme of energy metabolism, including phosphofructokinase, aconitase, and the electron transport complexes. Deficiencies of KGDHC are likely to impair brain energy metabolism and therefore brain function, and lead to manifestations of brain disease. In general, the clinical manifestations of KGDHC deficiency relate to the severity of the deficiency. Several such disorders have been recognized: infantile lactic acidosis, psychomotor retardation in childhood, intermittent neuropsychiatric disease with ataxia and other motor manifestations, Friedreich's and other spinocerebellar ataxias, Parkinson's disease, and Alzheimer's disease (AD). A KGDHC gene has been associated with the first two and last two of these disorders. KGDHC is not uniformly distributed in human brain, and the neurons that appear selectively vulnerable in human temporal cortex in AD are enriched in KGDHC. We hypothesize that variations in KGDHC that are not deleterious during reproductive life become deleterious with aging, perhaps by predisposing this mitochondrial metabolon to oxidative damage.

www.arclab.org/medlineupdates/abstract_10672230.html

Thought this to be of interest.

Richard

Richard,

Thanks for the post. I've read a little about alpha ketoglutarate but have limited myself to cofactors for these enzymes in my search to understand the physiology of LAF. They are more susceptible to dietary indiscretions/habits v. the enzymes themselves which are more subject to genetic input (or lack thereof). At least that's been my past approach. But thanks for giving me additional reading for the weekend (as if I didn't have enough already).

Condolences on the recurrence of AF. Don't be discouraged. Look at each episode as an opportunity to study it some more. At the very least it's an opportunity to indulge in some potential triggers, i.e., chocolate, alcohol (which I abhor), a late large dinner out, etc. All those other LAFers that are presently AF free have to stick to the straight and narrow.

By the way do you work out and if so what is your schedule for it?

PC, MD v54

PC,

The only trigger that I can surmise, is that late night apple. Will eliminate that. As for working out, I have been walking on the treadmill for 30 min. daily, or a good round of 18, walking. I will continue on my protein/veggie only diet, and after a few more days of steak only, as protein, will try fish again and see what that does to my indigestion. Still losing weight, though. 5'11" 163#s. The lowest I've been in 20 yrs. I have a weight room full of Nautilus, but a little apprehensive of using at the present, but as I better my diet, will try that again, but no power lifting. Thank you for your concern and thoughts.

Richard

Richard,

Almost exactly my height and weight as well. Did you workout later (or play golf later) yesterday? I find that about 3-3.5 hours after a good workout (same time of day for at least a week) my HRV becomes elevated (averaging above 30 ms) to the point where I become aware of increased ectopics. This at risk period goes on for about 90 minutes to 2 hours. Then my HRV drops back to normal (10-20 ms for me) after that (no change in activity) and I'm in the clear. Taking cayenne pepper or coffee or ginger root may help protect me during this at risk period. But I'm just experimenting on that. This is the silver lining to having episodes more frequently than monthly.

PC, MD v54

Declines in mitochondrial respiration during cardiac reperfusion: age-dependent inactivation of alpha-ketoglutarate dehydrogenase.

Lucas DT, Szweda LI.

Department of Physiology and Biophysics, School of Medicine, Case Western Reserve University, Cleveland, OH 44106-4970, USA.

We previously reported that cardiac reperfusion results in declines in mitochondrial NADH-linked respiration. The degree of inactivation increased with age and was paralleled by modification of protein by the lipid peroxidation product 4-hydroxy-2-nonenal. To gain insight into potential sites of oxidative damage, the present study was undertaken to identify specific mitochondrial protein(s) inactivated during ischemia and reperfusion and to determine which of these losses in activity are responsible for observed declines in mitochondrial respiration. Using a Langendorff rat heart perfusion protocol, we observed age-dependent inactivation of complex I during ischemia and complex IV and alpha-ketoglutarate dehydrogenase during reperfusion. Although losses in complex I and IV activities were found not to be of sufficient magnitude to cause declines in mitochondrial respiration, an age-related decrease in complex I activity during ischemia may predispose old animals to more severe oxidative damage during reperfusion. It was determined that inactivation of alpha-ketoglutarate dehydrogenase is responsible, in large part, for observed reperfusion-induced declines in NADH-linked respiration. alpha-Ketoglutarate dehydrogenase is highly susceptible to 4-hydroxy-2-nonenal inactivation in vitro. Thus, our results suggest a plausible mechanism for age-dependent, reperfusion-induced declines in mitochondrial function

and identify alpha-ketoglutarate dehydrogenase as a likely site of free radical-mediated damage.

PMID: 10359773 [PubMed - indexed for MEDLINE]

Richard

I thought this to be a very interesting study:

Mol Cell Biochem 2003 Jan;243(1-2):55-64 Related Articles, Links

Involvement of oxygen free radicals in the respiratory uncoupling induced by free calcium and ADP-magnesium in isolated cardiac mitochondria: comparing reoxygenation in cultured cardiomyocytes.

Meynier A, Razik H, Cordelet C, Gregoire S, Demaison L.

INRA, Unite de Nutrition Lipidique, Dijon, France.

Recently, we have observed that the simultaneous application of free calcium (fCa) and ADP-magnesium (Mg) reduced the ADP:O ratio in isolated cardiac mitochondria. The uncoupling was prevented by cyclosporin A, an inhibitor of the permeability transition pore. The purpose of this study was to know if the generation of oxygen free radicals (OFR) is involved in this phenomenon and if it occurs during reoxygenation (Reox) of cultured cardiomyocytes. Cardiac mitochondria were harvested from male Wistar rats. Respiration was assessed in two media with different fCa concentrations (0 or 0.6 microM) with palmitoylcarnitine and ADP-Mg as respiration substrates. The production of Krebs cycle intermediates (KCI) was determined. Without fCa in the medium, the mitochondria displayed a large production of citrate + isocitrate + alpha-ketoglutarate. fCa drastically reduced these KCI and promoted the accumulation of succinate. To know if OFR are involved in the respiratory uncoupling, the effect of 4OH-TEMPO (250 microM), a hydrosoluble scavenger of OFR, was tested. 4OH-TEMPO completely abolished the fCa- and ADP-Mg-induced uncoupling. Conversely, vitamin E contributed to further decreasing the ADP:O ratio. Since no hydrosoluble electron acceptor was added in our experiment, the oxygen free radical-induced oxidized vitamin E was confined near the mitochondrial membranes, which should reduce the ADP:O ratio by opening the permeability transition pore. The generation of OFR could result from the matrix accumulation of succinate. Taken together, these results indicate that mitochondrial Ca uptake induces a slight increase in membrane permeability. Thereafter, Mg enters the matrix and, in combination with Ca, stimulates the isocitrate and/or alpha-ketoglutarate dehydrogenases. Matrix succinate favors oxygen free radical generation that further increases membrane permeability and allows respiratory uncoupling through proton leakage. To determine whether the phenomenon takes place during Reox, cultured cardiomyocytes were subjected to hypoxia and Reox. 14C-palmitate was added during Reox to determine the KCI profile. Succinate had not increased during Reox. In conclusion, calcium- and ADP-Mg-induced respiratory uncoupling is due to oxygen free radical generation through excess matrix accumulation of succinate. The phenomenon does not occur during reoxygenation because of a total restoration of mitochondrial magnesium and/or ADP concentration.

PMID: 12619889 [PubMed - in process]

Richard

Fellow fibbers,

I'd like to follow Fran's lead in thanking Hans for providing the Conference Room. It is much appreciated by me to be able to connect with such a select group of LAFers.

On 03-20-03 21:34 below I posted some diseases/symptoms that Vit B6 deficiency has in common with Mg deficiency. You may have glossed over a seemingly insignificant one in hyperacusis (increased sensitivity to sound). This symptom has been described as audiogenic shock in the Mg deficiency literature (1). I know several on this board have mentioned this as a symptom (I seem to recall Lorraine talking about this). There appears to be connection between free glutamate and LAF. The probable/possible mechanism for this is through its role as the neurotransmitter for the ANS. Many LAFers may be deficient in either Mg, Vit B6 or P, all of which are required for the rate limiting step in metabolizing glutamate to GABA (a decarboxylase enzyme). Glutamate is excitatory and GABA is inhibiting. Therefore, I decided to look more closely at glutamate wrt hearing.

The eighth cranial nerve has two branches, auditory (hearing) and vestibular (balance). Glutamate is the main excitatory neurotransmitter in both the auditory and vestibular afferents (sensory nerve fibers). Thus, there appears to be a connection between glutamate sensitivity and hyperacusis or audiogenic shock. Salicylate (aspirin) recently was shown to facilitate the excitatory effects of glutamate in the cochlea (ear) (2).

Furthermore, in addition to balance the vestibular branch controls the eyes to maintain fixed point during head movement. Vestibular dysfunction, as in excess glutamate, results in nystagmus (lateral "spasm" of the eyeballs). I believe Mike F. was once told he had this.

A google search of "audiogenic shock" and glutamate comes up negative. I believe that modern medicine has not yet connected the dots wrt glutamate and Mg deficiency.

I don't think I have audiogenic shock, but my sense of hearing is my most acute sense. Furthermore, there has been a recent deterioration in my sense of balance.

You may also have read Richard's recent post about being able to terminate an episode within 30 minutes on occasion simply by drinking a "phosphorus drink". I believe that this mechanism is via pyridoxal 5 phosphate (see below posts). So tonight, when my HRV was inappropriately high and HR was inappropriately low, I decided to try this approach. While out for dinner with my wife I ordered a nice steak and a Coke. The effect was rather remarkable. Within 20 minutes my HRV dropped and HR increased. It has stayed that way for the past 2.5 hours. I find this rather exciting.

Your feedback would be greatly appreciated.

PC, MD v54

P.S. Any recommendations for a better P drink would also be greatly appreciated.

(1)FAO/WHO expert consultation on human vitamin and mineral requirements, p. 224 of Chapter 14, Magnesium

<http://www.micronutrient.org/idpas/pdf/846.14-CHAPTER14.pdf>

(2) http://www.iths.net/abstracts/selected_abstracts01.htm

Hi PC - Since my only technical knowledge is in geology, I don't often read the conference room posts so I'm glad you reached me on the BB.

My startling was not only a response to sound, but also to surprise, and also from apparently nothing at all. It was never a really strong reaction, but would sometimes occur several times in one minute which seemed strange. It seemed I could pretty much bring it on myself by just thinking about it. The startling really only occurred twice (both in the last year since the onset of AF) and lasted on and off for about a week both times. Otherwise only an occasional startle.

I've taken Solgar B-Complex for years, which includes 100mg of B6. In the past 6 months since my first startle experience, I've taken two daily (200mg B6/day). I've also taken 650-750mg magnesium glycinate for about 6 months and 1 - 1 1/2 liters WW/day. I've never taken supplemental phosphorus or intentionally tried to get it in my diet, so I have no idea why my intracellular level of it is somewhat high 17.5 (range 14.2-17.0). Do you have any suggestions why it would be high? The only intracellular ratio that is off is phosphorus/calcium which is low: 3.2 (range 3.5-4.3). My calcium is 5.5 (range 3.2-5.0) and magnesium is mid range.

Hope this covers the information you were looking for.

Lorraine

PC - In reading your post more carefully, I guess I should add that I have not noticed any imbalance, or eye spasms. As for my sense of hearing, I am definitely sensitive to sound even when I don't startle.

Lorraine

PC & Lorraine,

I am also sensitive to sound. I have to put plugs in my ears when attending movies-esp the previews. I end up take them in and out during the movie depending on the sound levels.

Rick S. 53,AMAF

Hi PC and Fran,

Thought this to be of interest:

"Levels of α -ketoglutarate (α -KG) can serve to mark an aspect of the carb. and fat metabolic relationship. When metabolic conditions, such as insulin intolerance, act to stimulate fatty acid synthesis, the rising levels of palmitoyl-CoA cause an effective inhibition of glutamate dehydrogenase. Since the dominant pathway for α -KG formation is production from glutamate by the activity of glutamate dehydrogenase, mitochondrial α -KG is depleted. To state the corollary, low α -KG is a marker for up-regulated fatty acid synthesis, increased palmitic acid in plasma and cell membranes, and increased serum triglycerides."

Richard

Richard,

The problem with VMAFers and possibly also with some AMAFers is glutamate decarboxylase. This is one of 112 enzymes (out of 3870) in the body that also requires P5P (and Mg or Zn) in order to function. These enzymes are very susceptible to polymorphism, which is a fancy word to mean that they can undergo a small mutation at a single amino acid that can easily affect its affinity for the cofactor, in this case P5P. This is the hot topic in genomics and Jackie hit the nail on the head when she wrote about biochemical individuality on the regular BB. Polymorphism is very common in the general population (check it out on a Google search) and pyridoxal phosphate (P5P) is at the top of the list. Because these cause only minor changes in coenzyme affinity one can get around the problem by loading up on the coenzyme (Km factor related). For two days now I've been taking 400 mg of B6 (half as P5P and half as inactive B6 in a B complex vitamin). This has essentially created a more vagolytic environment for me. My HR is about 10-15 beats higher and my HRV is about 10-15 ms lower than normal given the same kind of activity. This is because the neurotransmitter substance for the vagus nerve (glutamate) can now be broken down much more effectively. All that extra P5P enables the glutamate decarboxylase to do its job, as if it were normal. This means less glutamate and more GABA.

My sleep has improved presumably due to the greater levels of GABA.

My leg cramps have also diminished but I haven't worked out the biochemistry/physiology on that yet.

PC, MD v54

Hi PC,

I'm still trying to figure all this out, and it is quite complicated, but here is another explanation of glutamic acid, that might help, from the same book.

"Glutamate carries nitrogen from exercising muscle because the various amino acids, from degraded muscle proteins, transfer their amino groups to α -KG. The first step in degradation of excess amino acids in the liver also leads to production of glutamic acid due to the same transaminase enzymes. The nitrogen (or ammonia) from the original amino acids is then transformed into urea in the liver using the enzymes of the urea cycle. The glutamic acid becomes α -KG, which can be used as an energy source by entry into the Citric Acid Cycle."

Figure 4-8 Glutamate In Amino Group Cycling:

Asp + α KG AST/P5P to Oxaloacetate + Glu

Ala + α KG AST/P5P to Pyruvate + Glu

Glu GDH/NAC to α KG + NH₄

"Glutamate is the principal excitatory neurotransmitter in the brain. 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."

"Glutamic acid is also important in ammonia detoxification in the brain where it combines with ammonia to form glutamine."

As for GABA:

"The synthesis of GABA in muscle tissues from glutamic acid and ornithine is the most likely source of plasma GABA. Higher plasma levels probably reflect low conversion to succinic acid for

utilization by the Citric Acid Cycle and energy generation. Therefore, high plasma levels indicate potential inadequate energy generation in muscle and possibly other tissue. aKG and B6 are cofactors in this GABA metabolic pathway and can be used to alleviate this metabolic impairment and optimize cellular energy generation."

Richard

Richard

Very interesting. I haven't come across a-ketoglutarate (a-KG), so I can't say anything on the subject. I do know, however, more than B6 is needed to make GABA from glutamate. Do you know what food sources a-ketoglutarate (a-KG) is synthesised from?

I find the reference to the citric acid cycle interesting, though I have not fully understood it. I react very strongly to citric acid when it is used as an additive and have to avoid it (this may be because processed citric acid is made from corn). So somewhere, somehow, it is all tied in together. The way the body works is so complex and so co-dependant on a rich variety of other enzymes, vits and minerals etc, types and strains that science has yet to discover. It was for this very reason that I decided if anything was going to help me it was a high variety diet very low on free glutamate and carbs. That way my body would be getting optimum nutrients with the best chance of repairing itself. So far Brilliant.

PC

I am interested in the P5P and B6 increasing your heart rate taking you further away from the vagolytic state. Do you think this would affect blood pressure too? I haven't as yet decided whether to try this as a supplement as my diet works very well. But my blood pressure is stuck on low and my heart rate is also low too. Maybe just the kickstart I need.

Do you envisage that to rectify the problem with GABA production from glutamate one would need to take P5P and B6 for life?

Fran

Fran,

I plan to post in depth on this shortly, but to directly answer your question:

Yes, I'd envision taking B6 (or better yet its active form P5P) for life. As one became less symptomatic, the dose could be tapered, but unless one has a diet like yours, I don't think you could completely stop.

I don't think it would increase your BP, because it's just affecting your SA node. But I've never measured my own since starting mega-doses of P5P.

And regarding your statement:

"I do know, however, more than B6 is needed to make GABA from glutamate".

I think this is absolutely correct. If you look closely at the website on alpha keto glutarate that Richard was so kind to pass on, you see that its author recommends B6 and aKG for this chore. Taking aKG forces the glutamate reaction to go the other way toward GABA. B6 facilitates this.

I'm still working on my more detailed post and hope that Hans will keep the Conference Room door on glutamate open just awhile longer.

PC, MD v54

PC

Audiogenic shock was a nightmare for me. Something that I definitely have put down to excess glutamate. It has completely gone now. One thing since stopping free glutamate and going low carb is a paroxysmal hollow sounding in my ears. Sort of like when you speak it sounds hollow and echoes. Not very nice. I remember I suffered this many years ago before I got AF. I am wondering if this has anything to do with P5P.

Did you find a drink or something naturally high in phosphorous. I can only eat so much oily fish etc to get my phosphorous and will not take fizzy drinks like coke because of the free glutamate and sugar content. As ever I am too afraid to get into the supplement cycle, but may try it at some point in the future if I can't find a natural way to help it.

Fran

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.

The Facts

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 and was pioneered 30 years ago in Saskatchewan by two Canadian physicians, Doctors Abram Hoffer and Humphrey 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 job 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 Metamatrix, 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.metamatrix.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 (efferents) 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.
