

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

VIRTUAL LAF CONFERENCE

Proceedings of 16th Session
November 1st –

SUBJECT: Methionine (Sulfur) Acetylcholine Glutamate

Hans,

I've been reading about acetylcholine and glutamate, as you know, on the latter. I'm not ready to present my findings, but I'm beginning to believe that adrenergics are suffering from acetylcholine problems, mixed are suffering from glutamate and acetylcholine problems (me), and vagals are suffering from glutamate. This is all a guess, but I still believe methionine is a major player in all instances, coupled with Mg. and the typical cofactors so often discussed. I know you had mentioned an interest in the past on NO, so I thought, since I ran across this study, I'd share it now. You may have already seen it, however.

<http://www.jphysiol.org/cgi/reprint/535/2/507.pdf>

Molybdenum, folic acid, B12, and methionine deficiencies, coupled with the MSG reaction, have opened up some new research avenues for me. I don't know if there is a correlation between glutamate and acetylcholine inside the cell, as I know so very little about all this, but I'm trying to learn. As mentioned earlier, David S and I are both low in lithium, as well, so I'm trying to find a correlation here. I thought I'd try to spur some interest here, as it's been so quiet, and I'm running out of info. specifically on molybdenum. Hans, have you ever had a vitamin analysis done, and do you incorporate choline into your diet daily, by way of lecithin or eating eggs? Thank you.

Richard

Here's a study on lithium and glutamate, that was a bit difficult to completely understand, but I found of interest.

ABSTRACT

The role of transporters in clearing free glutamate from the synaptic cleft was studied in rat CA1 hippocampal neurons cultured on glial microislands. The time course of free glutamate in the cleft during a synaptic event was estimated by measuring the extent to which the rapidly dissociating AMPA receptor antagonist kynurenic acid (KYN) was replaced by glutamate during a synaptic response. Dose inhibition of the AMPA receptor EPSC by KYN was less than predicted by the equilibrium affinity of the antagonist, and the rise time of AMPA receptor miniature EPSCs (mEPSCs) was slowed by KYN. Both results indicated that KYN dissociated from AMPA receptors and was replaced by synaptically released transmitter. When transporters were blocked by D,L-threo-hydroxyaspartic acid (THA) or Li⁺, the mEPSC rise time in the presence of KYN was slowed further, indicating that transporters affect the glutamate concentration in the first few hundred microseconds of the synaptic response.

The glutamate transient necessary to cause these effects was determined by developing a detailed kinetic model of the AMPA receptor. The model replicated the effects of KYN on the amplitude and rise time of the synaptic responses when driven by glutamate transients that were similar to previous estimates (Clements et al., 1992; Clements, 1996). The effects of THA were replicated by slowing and enlarging the slower phase of the dual component transient by about 20% or by prolonging the single component by almost 40%. Because transport is too slow to account for these effects, it is concluded that transporters buffer glutamate in the synaptic cleft.

And:

Extracellular Li⁺ blocks transport by acting as a competitive antagonist at the Na⁺ binding site (Peterson and Raghupathy, 1974). The effect of Li⁺ on glutamate binding to the transporter has not been studied directly, but a previous report suggests that it decreases glutamate binding considerably, with no effect on AMPA receptor kinetics (Tong and Jahr, 1994b).

<http://www.jneurosci.org/cgi/content/full/17/12/4672>

Richard

Richard,

Thank you for alerting me to the interesting paper on NO. I am adrenergic and have actually experimented with trying to increase my NO level through supplementation with resveratrol and l-arginine. I did not observe any improvements. However, increasing the NO level in the myocardium, specifically the left atrial appendage, maybe beneficial in that it would reduce the risk of blood clot formation.

I have not had my vitamin levels checked and am not consciously trying to increase my choline levels. Perhaps I should be :-)

Hans

Hello to All,

I haven't had a lot of time to put this all together, but I want to share some points I have analyzed, based on my own testings, and observances of AF/flutter episodes.

Most of my episodes seemed to happen when either walking up a hill, or playing golf, but the last 3 have happened when either eating out (once) or consuming MSG (twice), while taking flecainide, a sodium channel blocker. Episodes, pre-diagnosis, pre-meds, were always under exertion, so I believe drugs can distort what the body's really doing, especially beta blockers, in my case. The betas left my body with absolutely no energy to perform its functions, hence that is why I stopped.

I wasn't a heavy exerciser, as some here are, but I did have digestive problems, that many of us share. In any case, either the digestive problems can cause malabsorption of important nutrients, or strenuous exercise can cause over usage of energy stores, with both leaving the body in a compromised position of energy output, being that the body doesn't have the tools to continue to run properly, specifically ATP.

A while back, both PC and I tried drinking a coke to convert our episodes, which worked in about 30 minutes. I came to the conclusion that it was the phosphoric acid in the coke, due to the fact that my serum test had shown low in phosphorous. Many have had temporary success with Mg glycinate, which I believe the glycine has equal importance, as well as the Mg. Many of us have consumed mountains of supplements, which have given temporary relief, only to falter back to the same old issue of AF, but maybe a bit better.

My conclusion is: ATP; Adenosine triphosphate. The one thing that is produced for the needed energy to run our bodies, morning, noon, and night. Mg, along with the B vitamins, phosphorous (in the coke), and the missing nutrient,

that we haven't given a lot of attention to; SAME; s-adenosyl-methionine, are all necessary for this conversion. The people here, who are trying to eliminate their AF have been taking the vitamins, minerals, and various aminos with some success, but the all important methionine is being left out.

My body stores were low, both in serum and urine, of all sulfur containing aminos, but why was that? I had changed my diet to organic meats, salads, eggs, nuts, and vegetables. I was especially lacking folic acid and B12, so if methionine was there and not converting to SAME, then my homocysteine levels should have been high, but they were at the lowest on the scale. That tells me one of two things. One, I wasn't getting any methionine in my diet, or two, that I was using it up as fast as I could consume it. I have to assume it was the latter.

Let's look at what James South said again:

However, 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. (1-3) After the neuron has fired, membrane pumps then pump the excess sodium and calcium back outside the neuron. (15) This is necessary to return the neuron to its resting, non-firing state. Neurons in a resting state prefer to keep calcium inside the cell at a level only 1/10,000 of that outside, with sodium levels 1/10 as high as outside the neuron (15) These pumps require ATP energy to function, and if neuronal energy production is low for any reason (hypoglycemia, low oxygen, damaged mitochondrial enzymes, serious B vitamin or CoQ10 deficiency, etc.), the pumps may, gradually fail, allowing excessive calcium/sodium build up inside the cell. This can be disastrous. (1-3)

<http://www.smart-drugs.net/ias-excitotoxins.htm>

Now let's look at some excerpts by Marios Kyriazis M.D.:

SAME (pronounced 'sa-me' as in the name 'Sammy') has been hailed as the safest and most effective natural antidepressant ever used. The full name is S-adenosyl-methionine and it is a molecule derived from the union of the amino acid methionine to a factor responsible for energy production, called adenosine triphosphate (ATP). The production of SAME from these two molecules is under the control of the enzyme MAT (methionine adenosyl transferase) (1).

SAME is the most important methylating agent in the brain. It is a methyl donor meaning that it provides methyl groups (essential factors needed for optimal health) to proteins, DNA and other molecules (2).

Methyl group deficiency has been blamed for causing depression and other brain or neuron diseases. Methylation is an essential process needed for maintaining active neurotransmitters, hormones, and phospholipids which help the brain remain in sharp condition.

Specifically, SAME increases the action of several neurotransmitters (dopamine, serotonin and norepinephrine for example) by facilitating the binding of these to cell receptors (3). It also increases the function of the cell membrane by boosting the production of an essential constituent, phosphatidylcholine. It stimulates polyamine synthesis which, in turn, enhance phosphorylation of proteins within the neurons, a therapeutic mechanism of many classic antidepressants. SAME helps maintain mitochondrial function at peak levels, thus increasing energy production in the brain. In addition, SAME has antioxidant properties, protecting brain tissues against damage from lipid peroxidation. Importantly, it also increases the production of the body's own glutathione which is a strong antioxidant involved in many brain processes (4).

Use under medical supervision. For best results it is recommended to also take TMG (trimethylglycine) 500mg-2000mg twice a day (which increases the metabolism of SAME), and- also co-factors such as folic acid up to 1mg per day, vitamin B6 up to 100mg per day, and vitamin B12 1mg per day. These will prevent SAME from being metabolized into harmful homocysteine and will help re-methylate homocysteine back to SAME, so they may be useful in those who want to reduce the dose of SAME; and still get the full benefits.

<http://www.smart-drugs.com/ias-depression-SAMe.htm>

Notice the importance of trimethylGLYCINE, and what would happen if one was lacking in B's and folic acid, of which was not my problem, because I had low homocysteine.

I can't copy this any info from this link, but it show the importance of SAME in the methylation process of choline.
<http://books.nap.edu/books/0309065542/html/393.html#pagetop>

It is my understanding that acetylcholine is like an excitory response in the cell, which communicates the opening of the ion channel to let in calcium and sodium, which in a vagal's case wouldn't be good, because it's overstimulating the vagus nerve. It must not be for me, because sodium channel blockers are working. I had thought there was a possibility that organophosphates could be a problem for me, because they block cholinesterase, which removes acetylcholine from the synaptic cleft. Being that I was experiencing more episodes of AF/flutter while playing golf, and the usages of organophosphates on golf courses, led me to this conclusion. It's either the effects of organophosphates blocking cholinesterase or my ATP isn't keeping up with my energy output. Read on:

The signs and symptoms are similar for carbamates and organophosphate poisonings. These pesticides combine with cholinesterase at nerve endings in the brain and in the tissues of the body, thereby permitting the accumulation of acetylcholine. The occurrence of symptoms is primarily dependent upon the rate of cholinesterase decline. Most differences are due to the fact that cholinesterase reactivation is much more rapid after carbamate exposure than it is after organophosphate exposure. After carbamate exposure, cholinesterase recovery may take from several hours to several weeks, depending on the degree of exposure. Also, the dose necessary to produce incapacitating symptoms is generally far from the lethal dose for carbamates, while the two doses are often quite close for organophosphates.
<http://pmep.cce.cornell.edu/facts-slides-self/facts/gen-posaf-chol.html>

Acetylcholinesterase: The enzyme that breaks down acetylcholine into choline and acetate or acetic acid. It is located in the synaptic cleft.
<http://www.neurosy.org/glossary%5ba-m%5d.shtml>

Here's more on the importance of ATP in regards to acetylcholine/cholinesterase:
In vertebrate neuromuscular junctions, ATP is stored at the motor nerve terminals and is co-released with acetylcholine during neural stimulation. Here, we provide several lines of evidence that the synaptic ATP can act as a synapse-organizing factor to induce the expression of acetylcholinesterase (AChE) and acetylcholine receptor (AChR) in muscles, mediated by a metabotropic ATP receptor subtype, the P2Y1 receptor. The activation of the P2Y1 receptor by adenine nucleotides stimulated the accumulation of inositol phosphates and intracellular Ca²⁺ mobilization in cultured chick myotubes. P2Y1 receptor mRNA in chicken muscle is very abundant before hatching and again increases in the adult. The P2Y1 receptor protein is shown to be restricted to the neuromuscular junctions and colocalized with AChRs in adult muscle (chicken, Xenopus, and rat) but not in the chick embryo. In chicks after hatching, this P2Y1 localization develops over ~3 weeks. Denervation or crush of the motor nerve (in chicken or rat) caused up to 90% decrease in the muscle P2Y1 transcript, which was restored on regeneration, whereas the AChR mRNA greatly increased. Last, mRNAs encoding the AChE catalytic subunit and the AChR -subunit were induced when the P2Y1 receptors were activated by specific agonists or by overexpression of P2Y1 receptors in cultured myotubes; those agonists likewise induced the activity in the myotubes of promoter-reporter gene constructs for those subunits, actions that were blocked by a P2Y1-specific antagonist. These results provide evidence for a novel function of ATP in regulating the gene expression of those two postsynaptic effectors.
<http://www.jneurosci.org/cgi/content/full/21/23/9224>

So it has to be ATP or organophosphates, but I don't think it's the latter any longer, mostly due to the flutter experience with monosodium glutamate. From what Joe South said, glutamate toxicity is mostly due to a lack of ATP. The body can't keep up with the energy output to remove MSG from the synaptic cleft.

If s-adenosyl-methionine is so important to, not only ATP production, but to the ever important antioxidant, Glutathione (made from a combination of glycine, glutamate, and cysteine), then why wouldn't we all want to incorporate this into our daily regimen. What would we have to lose? In the case of Jackie using MSM (methylsulfonylmethane), I wonder if this would give the same benefit as methionine. MSM helps methionine, but what if the latter is lacking.

Here's a bit more in relation to cell permeability and insulin:

Cell Membrane Permeability

All cells (and all organelles within cells) are surrounded by membranes. A membrane consists of two layers of molecules situated opposite of one another and consisting of an essential fatty acid on one end, and a sulfur containing amino acid on the other end. The amino acids are interconnected in such a manner that they form a surface into which

the proteins and other membrane constituents are inserted and secured. These proteins are necessary for the transport through the cell membrane of many types of nutrients and waste materials.

Sulfur bridges form flexible connections between the cells and the surrounding connective tissues. This allows the cells to retain their elasticity. When sulfur is in short supply, the cell wall hardens, and the cells lose their elasticity. The transport proteins of the membrane become locked, and the membranes become less permeable. This results in a reduced transport of oxygen and nutrients into, and excretion of waste products from the cells. This causes a shortage of oxygen and nutrients, and an accumulation of toxic metabolic waste products inside the cells. Reduced vitality and eventually degenerative diseases are the result.

Recent insight in free radical pathology has shown that the thiol (-SH) groups of sulfur containing amino acids can protect cell membrane protein chains from oxidation. But that is not all. Studies by Dr. Johanna Budwig have demonstrated that sulfur containing amino acids in cell membranes resonate with the double connections of the fatty acids, resulting in the release of electrons. Electron clouds are formed, which can move along the fatty acid chains. In this manner, electrical currents evolve which form the basis of all electrical energy in the body. This energy can be measured in heartbeat, nerve stimulations, muscle contractions, in short, in all chemical and electrical reactions which make life possible.

Metabolism

Enzymes are proteins which control all-important life functions. For example, they regulated all metabolic processes in our bodies. Sulfur bridges are responsible for the spatial structure of enzymes. Without sulfur bridges, enzymes would lack biological activity due to deviations in their spatial structure. Shortages in sulfur cause reduced production of biologically active enzymes, which result in a reduction of many metabolic processes. Sulfur is important for the cellular energy production in which glucose is metabolized under the release of energy.

Most important, sulfur plays a role in the electron transport system, as part of iron/sulfur proteins in mitochondria, the energy factories of the cell. Furthermore, sulfur participates in the vitamin-B Thiamine (B1) en Biotin. These vitamins are essential for converting carbohydrates into energy, by burning glucose. Insulin is a hormone excreted by the pancreas which mainly functions to regulate the blood sugar level. Insulin therefore plays an important role in the carbohydrate metabolism. Each insulin molecule consists of two amino acid chains, connected to one another by sulfur bridges (Figure 4). These sulfur bridges are very important for the proper functioning of insulin. Without these bridges, the hormone loses its biological activity.

<http://www.msm-info.com/>

And so, my direction is to avoid MSG and try to build up my stores of ATP, by whatever means necessary. Dr. Gersten didn't prescribe methionine by itself, but in addition to N-acetyl cysteine, taurine, and reduced glutathione that he did prescribe, I'm adding methionine, and making sure I get sufficient quantities of B12 and folate, along with all the other nutrients, such as B6/P5P and Mg.

I would also like to add, that while on beta blockers, and experiencing AF rather than flutter, I could have sworn I was vagal due to all episodes coming on at night, but past experiences, pre-meds, indicated I was adrenergic, because flutter always appeared during the day, and all three incidences of MSG toxicity occurred during the day. I know flutter is different than AF, but I have experienced both, with flutter being during the day, and AF being at night when on beta blockers. Maybe flutter is not classified as vagal or adrenergic.

Richard

I found this quite interesting, in regards to reducing platelet aggregation and increase in ATP. Here's some excerpts, but you might find it interesting to read in its entirety:

Steroid hormones play an important role in cholesterol metabolism. After all, cholesterol is a precursor to steroid hormones, including progesterone, cortisol, estrogen, and testosterone. In Denmark, testosterone has been used as a cholesterol-lowering agent for decades. They report the average reduction in serum cholesterol after testosterone initiation in males is about 25%. A 1972 World Health Organization (WHO) symposium also provided evidence that testosterone had cholesterol-lowering effects as well as increased clot dissolution, and reduced the adhesiveness of

platelets (by reducing the amount of the pro-aggregation effect of ADP). Testosterone also induced suppression of lipoprotein (a) levels (Marcovina SM in *Atherosclerosis* 1996; 122: 89-95). These are all traditional parameters of heart disease risk. Confirming the association between testosterone and heart disease, Gerald Phillips, M.D. at Columbia University Medical School, showed that men with the lower levels of testosterone had greater x-ray evidence of coronary artery blockage. Maurice A. Lesser, M.D. injected testosterone to 100 patients during an angina attack with "moderate to marked" improvement in 91%.

Testosterone shifts metabolism from an anaerobic state to an aerobic one by increasing the activity of enzymes in the Krebs cycle, which increases the level of ATP relative to ADP, which affords the changes mentioned above as well as a variety of other metabolic effects. Testosterone also balances glucose homeostasis by antagonizing glucocorticoids and insulin. It has also been shown "to have a direct effect on reducing blood sugar," in addition to lowering the insulin requirements of diabetics and improving insulin resistance (*J New Drugs* 1965; 5: 108-224). Testosterone therapy has been useful for a variety of degenerative conditions. Clearly, the notion that testosterone is merely a sex hormone is to discount the profound effects it has on metabolism – rather it should be considered an anabolic steroid in both males and females. Testosterone also stimulates protein synthesis and decreases protein breakdown leading to improved nitrogen balance. Some common clinical findings with testosterone insufficiency are fatigue, reduced muscle energy, decreased secondary sex characteristics, reduced temperature, reduced blood pressure, cold sweaty hands, frequent/excessive urination, anemia, and compensatory prostatic hypertrophy. The blood chemistry may show low phosphorus.

Another factor involved in the balancing role of testosterone is its relationship to saturated fat intake. In a study done in Finland, a diet containing only 25% saturated fat decreased testosterone levels by 15%. The same effect occurred when the ratio of polyunsaturated fats was increased compared to saturated fats.

It goes on to say:

Niacin is part of the alcohol insoluble and heat labile fraction of vitamin B (named the "G" complex that includes riboflavin, niacin, folic acid, PABA, choline, inositol, and betaine). As part of the "G" complex, it relaxes nerves and thereby acts as a vasodilator, helping selected individuals with hypertension and smooth muscle spasm without tone. According to *Compiled Notes on Clinical Nutritional Products* by Wally H. Schmitt Jr., D.C. (1990) and *Vitamin News* (1952), signs of "G" deficiency include:

According to Robert Peshek, DDS the "G" fraction of B-complex allows chloride to enter the cell, just as Valium does. Also raises cholinesterase levels. In fact checking the level of rbc-cholinesterase levels can be a guide to functional need for "G."

Cardiovascular - tachycardia, extra ventricular beats (PVC's), angina pectoris, and pre-myocardial infarction

Psychological - excessive worry, apprehension, moodiness, depression, suspicion

Digestive – insufficient stomach acid production and excess alkalinity, spastic gall bladder

Liver – cirrhosis and loss of fat metabolism activity, deficient formation of Yakitron, a physiologic anti-histamine

Neurological – insufficient acetylcholine activity and cholinesterase activity (for breaking down acetylcholine and for recycling choline), restless, jumpy, or shaky legs, body or limb jerks upon falling asleep, can hear heartbeat on pillow

Skin and mucous membranes – cheilosis (cracking at corners of mouth), friable skin, especially on face and neck (when shaving), bright red tongue tip, strawberry tongue (purple), loss of upper lip (thin upper lip), irritated mucous membranes of the rectum, vagina, and conjunctiva (frequent crying), excessive oil on face and nose, roughness, cracking and exfoliation of the soles of the feet, and psoriasis

Visual - burning or itching of eyes, photophobia (sun sensitivity), blepharospasm (eyelid spasms), blood shot eyes due to capillary engorgement, seeing only parts of printed words (circumcorneal injection), pallor of the temporal half of optic disc, transient ischemia of retina - like looking through a fish bowl

Endocrine – excess estrogen and menstruation, cystic mastitis or gynecomastia, premenstrual tension, and excessive adrenal function.

<http://www.drkaslow.com/html/cholesterol.htm>

Richard

Richard,

Perhaps I am not correlating this correctly, and I might be off base, but I would like to share my understanding on some of the dangers of methionine (or perhaps better termed...the inability to convert or revert methionine), as it relates to the heart, now that I am starting to grasp the fundamentals of amino-acids. Perhaps you have already discovered this and presented it, if so I apologize in advance.

The body's main supply of homocysteine is derived from the amino acid methionine. The over-abundance of homocysteine in the blood is a better indication of arterial wall damage and cardiovascular damage than just about anything else... according to a theory set forth by Dr. Kilmer McCully, a pathologist from the VA Medical Center in Providence, Rhode Island.

Fascinating to me is this: The amino-acid methionine is converted into homocysteine and... homocysteine cannot be converted to the amino-acid cysteine without B6,B12 and folic acid! And furthermore, Cysteine is a major component of the antioxidant, glutathione which contains binded glutamate.

Methionine can also be created by the conversation of homocysteine through folic acid. So again here we see that folic acid is a key player in regulation of the homocysteine levels.

Causes of Hyperhomocysteinemia

Vitamin Deficiency
Folate Deficiency
Vitamin B6 Deficiency
Vitamin B12 Deficiency
Chronic Disease
Chronic Renal Failure
Hypothyroidism
Psoriasis
Cancer
Tobacco abuse
Medications
Anticonvulsants
Methotrexate
Nitrous Oxide
Homocystinuria (Inherited)

This list obtained by FAMILY PRACTICE NOTEBOOK.

URL: <http://www.fpnotebook.com/CV241.htm>

Joe

Joe,

I absolutely agree, that folate and B12/6 have to be present. As you read above, my methionine levels in urine and serum were very low, but so were my homocysteine levels, as were my folate and B12. If I had enough methionine, but not folate, then I should have had high levels of homocysteine, but I didn't. That told me that I needed more methionine, along with taking N-acetyl cysteine and taurine. S-adenosyl-methionine (SAME) is required for the pathway

conversion to norepinephrine, which I also had a problem with, and for the making of ATP. I'm still studying to find more benefits. What I don't know is if cysteine or MSM can substitute for S-AdoMet. Methionine also makes cysteine, which attaches to mercury to form methylmercurycysteine to carry the mercury out of the body. It is extremely important, as you said, though, to make sure one has plenty of folate, B12 and B6, which I am taking in large quantities, that were prescribed by Dr. Gersten. Thank you for the reminder, and making that point clear to others.

Richard
