THE AFIB REPORT
Your Premier Information Resource for Lone Atrial Fibrillation
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VIRTUAL LAF CONFERENCE

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SUBJECT: Managing Afib – Are we getting close?

Recent postings concerning research and observations made by PC, Fran, Carol, Jackie, Richard, Michael in SF and many others have lead me to believe that we may be close to being able to formulate a regimen that will be effective in reducing the frequency and duration of afib episodes.

OBSERVATIONS

All seem to agree that a daily magnesium intake of about 800 mg (elemental) is crucial and that the magnesium should be taken in the form of Waller Water or magnesium glycinate (chelated magnesium). I have just checked my records and found that both Fran's and Erling's average total daily intake was a bit over 800 mg (930 and 850 mg respectively).

There are valid medical reasons why magnesium should be helpful as clinical trials have shown it to be highly effective in reducing PACs and PVCs. Poor absorption or excessive laxative effect is unfortunately, a big problem with most forms of magnesium so any regimen should standardize on either WW or magnesium glycinate (chelated magnesium) or a combination of both. Good brands of magnesium glycinate are Solgar and Metagenics in the US and Trophics in Canada.

PC's findings about the importance of proper hydration should of course, also be incorporated.
Aldosterone, which PC and I both believe is the main villain, is released when a shortage of water and/or salt (sodium, Na) is detected by the kidneys. Keeping constantly hydrated by drinking at least 2 liters of water throughout the day will help reduce the need for aldosterone release and thus keep levels lower. It is interesting that hydration does not seem to decrease PACs and PVCs (observed by both PC and myself) but does decrease episode frequency.

A low salt diet could presumably also be a trigger for the release of aldosterone. I eat a fairly low salt diet so I add ¼ teaspoon (1.5 gram) of Celtic sea salt to each liter of water. Celtic sea salt contains 31% sodium (Na) as well as about 80 other trace minerals. So ¼ teaspoon would provide 465 mg of Na. Drinking 2 L of Celtic sea salt fortified water would thus increase my daily sodium intake by about 900 mg. This should be viewed in light of current recommendations to keep Na intake below 2400 mg/day. So is adding Celtic sea salt a good idea or a bad idea?

Dr. F. Batmanghelidj, MD, the author of "Your Body's Many Cries for Water" recommends adding ¼ teaspoon of salt to every liter of water. He says that the body will start losing salt if relatively large quantities of water are ingested without a commensurate intake in salt (page 160). Dr. B also labels a salt-free diet as "utterly stupid". Clearly increasing hydration while losing salt may well be counterproductive as far as aldosterone suppression is concerned. It is also worth mentioning that Fran has reported that sodium is an insulin antagonist. As most afibbers tend to be perhaps too

quick on the draw when it comes to insulin release a little extra sodium may perhaps be beneficial. We need some clear and reasoned discussion to sort this one out!

Eating lots of fruits and vegetables should provide plenty of potassium. However, potassium is known to help reduce PACs and PVCs so is supplementation also in order and if so by how much? It should be kept in mind that high potassium levels cause the release of aldosterone so perhaps PAC and PVC control is best achieved through magnesium supplementation.

Stress has been mentioned by many as an important trigger for afib. It increases cortisol levels and causes the release of aldosterone via the ACTH pathway. Clearly, a consistent stress reduction program would be in order as part of the regimen.

HYPOTHESIS

Is there any scientific support for the findings that magnesium and water will reduce afib severity? To answer that question I would like to postulate a hypothesis somewhat similar to the one outlined in my play (See Session 2 of the Conference Room Proceedings)

Please bear in mind that much of what follows is speculation on my part – so here goes!

An afib episode can be viewed as involving four stages:

Triggering
Initiation
Propagation
Termination

The Triggering Phase
Here the autonomic nervous system, either the sympathetic branch (adrenergic) or the parasympathetic (vagal) branch is triggered into activating the dormant foci mostly situated at the junction between the left atrium and the pulmonary veins. Once the foci start firing the initiation phase begins.

The Initiation Phase
Here the foci (rogue cells) initiate PACs or PVCs (depending on location) and take us straight into the propagation phase. Two things should be noted here:

(1) Afib is not present until the propagation phase is reached. In other words if there is no trigger and no PACs or PVCs there will be no afib (this is where magnesium comes in). It is also true that 60% of the adult population experience PACs but does not experience afib. Clearly the important stage in afib itself is the propagation stage.

(2) I believe the triggering phase is the only phase that is different for adrenergic and vagal afibbers. The initiation, propagation and termination stages are the same irrespective of type of LAF.

The Propagation Phase
If 60% of the adult population experience PACs but only 1% experience afib what causes the PACs in one case to be harmless and in the other case to initiate afib? The answer, in one word:

INFLAMMATION

Several studies have shown that afibbers suffer from inflammation of the heart tissue. I believe inflamed tissue and its big daddy or perhaps I should say son, fibrosis, contains barriers that either misdirect normal impulses from the SA node to the AV node or alternatively provides pathways for aberrant signals originating from the misfiring foci. Either way, chaos (afib) is the result.

Next question of course: “What causes the inflammation?” Aldosterone is the prime candidate here. It is known to cause both inflammation and fibrosis in heart tissue. Can elimination of inflammation prevent afib? Absolutely! Dr. Andrea Frustaci has provided evidence that treatment with prednisone (a powerful anti-inflammatory) will eliminate AF.

So the idea of ameliorating afib through reducing aldosterone levels by increasing water and perhaps salt intake makes a lot of sense. It may also be beneficial to take a natural anti-inflammatory such as curcumin, boswellia or Moducare (plant sterols and sterolins) to further support the elimination of inflammation. Question: “What role if any, would spirinolactone or eplerenone play in this scenario?”

The Termination Phase
Most paroxysmal afib episodes terminate on their own. Why? As discussed in the Play, the violent shaking of the atrium releases copious amounts of ANP (atrial natriuretic peptide). ANP is a powerful anti-inflammatory and also promptly shuts down the production of aldosterone so it really and truly is the optimum “drug” for terminating an afib episode. Maybe the day will come when afibbers can keep afib at bay by periodic injections or ingestion of ANP similar to the treatment of diabetics with insulin.

Once the episode is terminated the heart is usually quiet until something builds up again and I believe that something is aldosterone.

OPTIMUM REGIMEN

So the main components of an optimum afib prevention regimen appropriate for all paroxysmal afibbers would seem to be:

Magnesium
Water (with or without sea salt)
Natural anti-inflammatory
Potassium (perhaps)
Stress Reduction

Digestion
As someone pointed out, magnesium glycinate is treated as an amino acid rather than as a mineral by the body. This means that the digestive system has to be up to snuff in order to benefit from taking it. As a matter of fact, I believe a lot of our problems are caused by the fact that many of us do not properly absorb all the good, organic food and high-grade supplements we present to our bodies. I have personally found that regular use of digestive plant enzymes and probiotics has made a tremendous improvement to my digestion and believe it will prove to be key in my eventual victory over afib. I’ll be happy to discuss plant enzymes and probiotics with anyone interested.

CONCLUSION

What we need now is a thorough discussion eventually leading to the adoption of a very specific protocol that we can all evaluate and compare the results of in an organized fashion.

Hans

Hans,

With respect to Magnesium supplementation, I have two questions:

1. You refer to dosage of 800 mg. (elemental mag.). In your book, you discuss the variable absorption levels of the different forms of magnesium supplements i.e. oxide, carbonate, orotate and citrate. Interestingly, I don't see specific numbers on glycinate. What is the amount of absorption of mag. glycinate? I use the Kal brand that has 400 mg. (as Mag. Glycinate) per two tablets. If you tell me that this will yield twenty percent absorption of elemental mag i.e. 80mg., then I assume I will have to take twenty tablets to get 800 mg. of elemental. I take far less than that which means it may be doing nothing.

2. I tried the Natural Calm powder form of mag. citrate. Although it did not cause PAC's or Afib, it caused an uncomfortable sensation in my heart which went away as soon as I stopped. Is it possible that tablets of glyinate could have different impact from the powder form of citrate? If not, then I guess I am one of the few who cannot tolerate the magnesium.

Kerry

Carole

It may be the citrate you were reacting too. Most forms of citrate are made from corn starch and as such can be a two fold problem for some. Corn allergy or free glutamate. I had AF reaction to Mg citrate and it was after this I decided to get all my nutrients from whole food form so I could be sure about everything I was consuming. It can't be magnesium I am allergic or intolerant to as get high amounts in my diet.

Fran

So are you saying that you do not take mag. supplements at all? Thanks for the tip on citrate.

Kerry

Sorry Kerry I called you Carole. No I don't take any supplements as they always seem to throw me off balance and more susceptible to AF. I may be more sensitive than the average Afibber, but it works this way for me. I just read up on what nutrients I need and plan my diet around that. eg oily fish everyday, pumpkin seeds, almonds etc for Mg. The only thing I lack in is vit D which is OK in summer as I get it from the sun. I get more the RDA for all vitamins and minerals - that is if I am absorbing them, which I believe I am.

Fran

Kerry,

Magnesium supplementation is too important to mess around with. The only brands that I recommend are Metagenics, Solgar and Trophics (in Canada). They are all chelated magnesium (Albion Process) which is magnesium glycinate made via a special patented process. They may be more expensive, but I believe they are worth it. They also have the advantage that they list their content of elemental magnesium, not magnesium glycinate. So if you take a 100 mg tablet you know you are getting 100 mg of elemental MG. So you need 8 tablets spread throughout the day.

Hans

Hans,

Great post. Three points:

1. Can't get Mag Glycinate anywhere here in the UK - my 2 choices are citrate and 'chelated' (unspecified) mag (both Solgar)..... which in your opinion should I go for?
2. I was recently diagnosed with gastritis (and have a long history of digestive woes) and, having recently purchased some plant enzymes, read on the tub that they should not be taken by someone with gastritis/digestive problems..... what do you reckon? Should I give 'em a go anyway (shucks, jut realised (having gone to look again at the tub) that I've thrown 'em away - should I get some more or avoid 'em as per the labelling?)?
3. I agree as regards the aldosterone issue - I know that I have had (and likely continue to have albeit in perhaps more

subtle ways) hormonal probs..... puberty delayed until age 17 plus excessive sweating under the arms age 17-19..... excessive aldosterone linked with an extremely violent and chronically stressful childhood and adolescence ??

Thanks again for all your continuing efforts on our behalf,

Mike F.

Mike,

Solgar chelated magnesium is magnesium glycinate made via a special patented process (Albion Process). As long as it says Albion Process on the bottle you are getting the right stuff.

Hans

Mike,

Sorry, I overlooked your second question. Yes, plant enzymes can be pretty rough on a sensitive stomach. I do however have a Canadian source of plant enzymes specifically for sensitive stomachs. Please send me an e-mail if you are interested.

Hans

I think the scenario above is getting very, very close. You don't mention anything specific with the triggering phase. I personally think (as you all know) that the triggering phase comes with an overload of free glutamate.

You end the hypothesis with "Once the episode is terminated the heart is usually quiet until something builds up again and I believe that something is aldosterone".

It could be, but I am wondering if aldosterone is only part of the picture. I would suspect that the triggering phase would also have a bearing on the end result. And am wondering what effect free glutamate has on aldosterone levels. Have done a 20 minute Google search and not come up with anything as yet.

The reason I wonder is presuming my aldosterone levels are now optimum due to good hydration, salt and minimum stress load etc, why would I still be at risk from ingesting free glutamate which is also known to overstimulate cells and cause them to fire erraticly?

Would spironolactone, an anatagonist of aldosterone have long term benefits or would one have to take it daily if aldosterone was permanently unbalanced due to long term dehydration and stress.

If anyone can discover if the glutamate pathway involves levels of aldosterone it may help with an answer (for me at least).

Fran

Mike

Just wondering how you manage with eating a papaya or paw paw fruit. These are great for digestion and are often used to tenderise meat due to high enzyme content. Pretty powerful fruit. I also learnt today that the seeds can be dried in the oven and ground like pepper for a great taste and is reputably good for arthritis.

Fran

With respect to the regimen for prevention of Afib, I have found that the daily intake of 4-5 grams daily of a combined EPA / DHA formula has been co-incident with a dramatic improvement in my Afib. I say co-incident rather than directly causative because I cannot be absolutely sure and I leave room for the possibility that my condition has simply gotten better. Nevertheless, I strongly suspect that the fish oils have been the cause of my improvement. I have gone from one episode every week to ten days to maybe one every two months. I take cardizem but it has no effect on the frequency of episodes. It simply keeps my heart rate lower in Afib. Given my improvement, I will be talking with my EP next week about eliminating it altogether, which will make aspirin the only drug I take on a daily basis. I use flecainide on demand. Conversion occurs after two doses over a twelve-hour period every time like clockwork.

I have read that fish oils have, in addition to the anti-thrombotic effects, anti-inflammatory and anti-arrhythmic effects as well.

Kerry

I have not made many comments on this page before but have been an avid reader. I have been on flec. For a couple of years and was on toprol which was hell. After reading about mag. and potass. I started taking 1000 mg. of mag and 200 mg. potass. A day. I cut back on the mag. to 750 Mg. do to the G.I. issues. I also take a mired of other supplements. The mag. I take is the Nature Made over the counter version. 250 Mg. tablets. It says it is mag. Stearate and it seems to be working. I am off toprol and afib free for 2 months. Are you saying this mag. will not work or what is the reasoning behind your comments?

Jack

Hans,

Once again all of us on the BB must offer our collective thanks for your tireless efforts unravelling this intricate ball of yarn. Once again we are the beneficiaries of your amazing powers of distillation.

Time will only tell where we are on this tortuous road, but I believe we're making a rather large stride in addressing not only maximizing (to bowel tolerance) the intake of Mg and K but ALSO minimizing its loss due to aldosterone. This oft portrayed "villainous" hormone usually gets overlooked in the in v. out equation. Not only does it result in the urinary loss of K but also Mg. It does no good to dine on bananas, fruits, vegetables, nuts and supplements such as magnesium glycinate as well, if we continue to excrete K and Mg in the urine.

Your "package" addresses this culprit by eliminating stress (adrenergic afibbers) and dehydration (vagal afibbers). I'm not quite sure where those with GERD fit in. They appear to me to be vagal afibbers. However, stress also increases the incidence of GERD. My belief is that they may slowly loose these two electrolytes in their urine via low grade metabolic alkalosis caused by the hypersecretion of gastric acid. There have been some recent posts on the BB about the mechanism for PACs and AF caused by the left lateral decubitus position (lying on ones left side). This is supposed to be a vagolytic position according to the medical literature. So I confess my ignorance on how this works. I'm similarly discomforted in this position and I'm definitely vagal. Perhaps there is some unappreciated connection here with GERD. Lying on ones right side enhances gastric emptying and therefore decreases gastric distention.

I've been so convinced of the involvement of aldosterone in all this that I've been taking spironolactone, an aldosterone antagonist, for quite a few months (up until a week or so ago). Toward the end I was more enamored of its possible blocking capability in the heart where aldosterone can cause inflammation and fibrosis. However, I have no idea if its cellular receptors in the kidney are the same as those in the heart. Not only are the organs different but one is epithelial and the other is mesenchymal. So they're probably not the same. Needless to say the cessation of spironolactone (peaks in two hours with a half life of 10-20 hours) has not in any way negatively impacted my AF free run. This AF free interval has persisted despite every effort on my part to trigger an episode, e.g., large late meals, sex, snorkeling, etc., all bonified reliable triggers for me.

Over the past two and a half years, during which time I have kept a detailed diary, I have had about 150 episodes of AF. Today represents 4 weeks without an episode, the longest AF free period for me in two years (all due to hydration - no meds, no supplements). Given the failure of spironolactone and the success of hydration, I think it is safe to say that it is much better to remove the stimulus for the secretion of aldosterone than to block its action. This basically underscores the difference in the approach to healthcare between alternative (hydration) and traditional (pharmaceutical) medicine.

I think Hans is right on the money in the inflammation connection with aldosterone again being the villain. My C reactive protein was modestly elevated when my AF episodes were occurring weekly. If this AF free interval continues I plan to soon repeat my CRP and possibly lend further support to Hans' proposed regimen. A second look at my intracellular K and Mg might further confirm this. My first intracellular mineral exam specimen was taken on a day that ended in AF.

I personally don't think there is a connection between glutamate and aldosterone. The former causes vagal tone and the latter causes intracellular K imbalance. My vagal tone has definitely not decreased, despite the presumed improvement in intracellular K. Both are required for AF. I plan to modestly increase the Mg in the waller water I make in an attempt to decrease my PACs.

Kerry has mentioned a perceived improvement in her AF status associated with fish oils. Just today I read an article entitled “Antiarrhythmic effects of omega-3 fatty acids: From epidemiology to bedside”, September 2003 * Volume 146 * Number 3, Progress in Cardiology.

I know that Erling highly recommends fish oils. I have no idea how this actually works wrt AF prevention.

Still so many questions, but a few answers are beginning to appear.

PC

Jack,

The reason I recommend chelated magnesium (magnesium glycinate) is that there are studies attesting to its superior bioavailability and that when the bottle says 100 mg it means that there is 100 mg of elemental magnesium in each capsule or tablet. Magnesium stearate on the other hand, only contains 4% elemental magnesium so a 250 mg tablet would provide only 10 g of elemental magnesium. I don't think that would be enough to make any noticeable difference. Also, stearic acid is a long chain saturated fatty acid, not very heart-friendly at all.

Hans

I think this is an excellent topic, and am very excited for the results that PC is experiencing:)))))) I have been incorporating more water in my daily regimen, and I must say, that I played golf the other day in record breaking heat, and even walked the course, (with my bottle of water in hand), and did not have a break through of AF or flutter. One of the guys I was playing with had to stop on the 12th hole, as he was too exhausted, but I continued. It got up to 95 degrees. I helped put up scaffolding that morning, for some painting being done in my home, and then went to my fantasy football league that night. I am taking no supplements presently, as I had been doing all those testings, and just didn't get back into taking them, until I spoke with Dr. Gersten. I hate swallowing all those pills. I am still on flecainide, so don't know if this is playing a role, but I think if I had not been drinking so much water, I would have gone into flutter.

As for my indigestion problem, that went away with the Paleo diet, and has not returned, I think this is playing a part for me, as well. I might add, however, that because I was eating salads three times a day and fruit, usually 2xs, the possibility of the water content could have been helping as much as the nutrients, but I had not thought about that until now. I was drinking more water than normal, however, but not to the extent that PC is now. Digestion needs an extreme amount of water for its process. I am a bit confused about GERD. I thought it was acid reflux, of which I had, but I now know that I did not have enough acid, so the food would sit in my stomach trying to digest, and the gas build-up would cause the acid to back up into my esophageus. So maybe someone could clarify that for me. I just assumed I

had GERD. As for hypersecretion of acids, I would think if one has AF, as well, they would need more water, too, and a better diet, especially in lieu of the fact, that much more water would be used for the hypersecretion, therefore diverting the limited water from other needy organs.

In the case of CRP, my levels were very low, and I had been in flutter for 1.5 mths, when this test was taken. I went into flutter on 4/1, upon stopping dysopyramide, and the test was taken on 5/14. I went back into NSR on 5/17 after giving flecainide a second, on demand attempt, of which I have kept taking continuously, since then. So go figure, on this one. Maybe the ANP was working.

The one time I went out of rhythm from 5/17 to present, was when I ate bean dip, with sour cream and cheese, and chips. I awoke the next morn. in flutter, and reverted back after taking an extra dose of flec. Was it the glucose in the carbs, possibly hidden MSG, or maybe that I didn't drink much water that day? Because I have eaten at restaurants frequently, I would have to guess it was my water intake. When at restaurants, I eat salads and fish or meat, and the salads have dressings and the meats are usually seasoned and I have had the occasional sugar containing dessert, with no problems. I have also had the occasional soda.

As for flec. working so well for me again, I have come to the conclusion that my diet has played a major role in that. Somehow flec. uses dopamine, and in the case of flec. overdoses, they administer dopamine, to counteract. Because of my high protein intake, I am making that assumption, based on my possible restoration of phenylalanine, which breaks down to dopamine. In eating more salads and vegetables, I have opened up that pathway, to better serve the effects of flec. Just my theory, however.

I have not worried about my salt intake in the past or present, and do salt all my meats. I use Johnny's Seasoning Salt, and it states it has no MSG. I should get the Celtic Sea Salt, but just have not done so. I found the Morton's Lite Salt to not be as good tasting on meats, so I only use it for other salting needs. I may not be doing the right thing, in the kind of salt I use, but my taste buds are winning this battle.

So in conclusion, I do believe water could very well be a major player here, especially in regards to myself, because I, like PC, was not much of a water drinker. I will continue on my path of taking whatever Dr. Gersten recommends and then will try to cut out flecainide and see what happens. I certainly hope this theory works for all concerned here. Maybe water is the true fountain of youth!!!!!

Richard

Richard,

I'm glad you again mentioned GERD. I also assumed I had some element of mild GERD, as I had occasional mild postprandial gastric distress. However, one thing I've noticed during this hydration kick is the complete absence of that distress. I think this is due to the fact that I now drink no fluids with my meals (no desire for them given my state of hydration), unlike before when this was definitely not the case. I suspect that previously I was diluting the gastric acid and hence its ability to digest gastric contents. Accordingly, there was probably more gastric distention (and vagal stimulation) and more metabolic alkalosis (more acid required to do the job of digestion). This latter no doubt further compromised K and Mg, since they both accompany bicarbonate into the urine in the process of returning blood pH to its tightly controlled range of 7.35-7.45.

One other thing I've noticed is that my leg cramps have worsened. I have no idea why. Like You, I'm starting to add salt to my Waller water.

PC

PC,

I have not had any problems with drinking during meals, since beginning the Paleo diet. I am not drinking WW, either. I'm taking no supplements, whatsoever. When I was taking Mg. alone, I began to have leg cramps, that I did not

experience before. I then started taking Ca/Mg. (Slow Mag) and the leg cramps went away, so I believe, at least in my case, that I needed calcium, as well. You might try taking Ca., but then I hate to see you upset your record. I might mention that I have pretty much eliminated dairy, so I felt I needed the calcium, and I felt the dairy was part of my problem, anyway. I have also been told that anytime one has leg cramps, they are lacking in Vit. D, but I don't have any info. to back that up, and you certainly would have enough of that from being in Hawaii, so that's probably not your problem. My daughter gets legs cramps from time to time and the Slow Mag does the trick. It contains 212mg Ca. carbonate and 128mg of Mg. chloride hexahydrate per 2 tabs.

I'm going to do some reading on glycine, as it is an inhibitory neurotransmitter amino, like GABA, and I did not know this until yesterday.
Could it be the glycine helping in the glycinate form, along with Mg.?
See page 5.
http://www.utoronto.ca/lsrnb/Current%20Research%20and%20Publications/Sleep_Breathing_Paper.pdf

Be well and stay AF free!!
Richard

Richard,

Thanks so much.

Perhaps my initial concern about Vit D increasing Ca more than Mg was overblown.

I'm about to request an intracellular mineral analysis and perhaps it would be best to do this before reintroducing Vit D. The leg cramps aren't really a problem, more of a curiosity.

I was at the movies again tonight and during some exciting sections experienced numerous PACs. In fact I was briefly in bigeminy. The rate (chronotropicity) was low but the force (inotropicity) was significant similar to what I often encounter during sex. This no doubt was due to catecholamines which have the same effect on the heart as dopamine. I'm sure that I would have gone into AF had this been before my hydration kick.

I find this all so fascinating because my PACs have definitely not decreased during activities that cause shortening of the refractory period (increased vagal tone and adrenergic tone both due this). The big question to me is just how does improved intracellular K (an assumption until the above test results are determined) protect against AF at such times? Hypokalemia does cause shortening of the refractory period, increases dispersion and increases automaticity. So perhaps it is a cumulative thing.

I promise to let everyone know when this AF free run ends. It undoubtedly will, but I don't think it will be anytime soon.

PC

PC

I am just trying to see a path through my question on aldosterone and free glutamate. I have found these similarities.

It is a known fact that MSG is a calcium channel opener, a sodium channel opener and a vasoconstrictor. Aldosterone is also a vasoconstrictor and a sodium channel opener. I assume that as they use calcium channel blockers to treat high aldosterone it is also a calcium channel opener. I think I would be right in assuming that both aldosterone and free glutamate would have similar side effects on blood pressure regulation and electrolytes. Not to mention the problems that stem from this. Of course MSG is known to excite the heart anyway, so I think that either could be the problem, or the trigger, and of course if one was a bit dehydrated and then ate free glutamate it would be a double whammy. And from this I think I have answered my own question.

Your professional opinion would be appreciated.

Thanks
Fran

Fran,

You always ask the most difficult questions, or at least ones for which I haven't the foggiest. My professional opinion should accordingly be given a commensurately low status.

I knew some of your stated facts, but you are certainly plowing new ground with me on others. What is so complex on exploring the aldosterone/glutamate connection, as you've stated it, is the cell receptors.
Not only might aldosterone receptors in the kidney be different from those in the heart and blood vessels, their function might be as well. I was only aware of glutamate receptors in neural tissue. I'm not sure how it works wrt vasoconstriction. Does it do this directly or through a nerve, either by inhibition of vascular relaxation of stimulation of vasoconstriction? Can it directly affect cardiac muscle cell receptors? If you find that glutamate is a Ca or Na channel opener in the heart, please let me know.

But aside from all these considerations and others, you may well have answered your own question. I can certainly speak from experience in that glutamate causes a sharp increase in my PACs. The magical waters of Lourdes uhhh Waller continue to work wonders for me.

PC

PC,

I purchased the book, "Your Body's Many Cries For Water", and upon skimming, found this to be of interest, in that it possibly pertains to you.

"Salt is a most essential ingredient of the body. In their order of importance, oxygen, water, salt, and potassium rank as the primary elements for the survival of the human body. It is said that salt crystals are naturally used to make bones hard. Thus salt deficiency in the body also could be responsible for the development of osteoporosis. Salt will be taken out of the bones to maintain vital normal levels in the blood."

"The precaution to keep in mind is loss of salt from the body when water intake is increased and salt intake is not. After a few days of taking 6-10 glasses of water a day, you should begin to think of adding some salt to your diet. (I think you mentioned you were doing this.) If you begin to feel muscle cramps at night, remember you are becoming salt-deficient. Cramps in unexercised muscles most often means salt shortage in the body. Also, dizziness and feeling faint might be indicators of salt and water shortage in the body. If such occasions arise, you should also begin to increase your vitamins and minerals intake--particularly if you are dieting to lose weight or do not eat properly, including vegetables and fruits for their water-soluble vitamin and mineral content. " pgs. 160-161

I had no idea that lack of salt could cause this. Thought I'd pass it along.

Richard

Richard,

I am in your debt for your diligent efforts on this BB to safeguard my (and everyone else's) health. Thank you so much.

I had no idea that salt could do this either. I've only heard that Mg, K or Vitamin B6 (pyridoxine) deficiencies could be specifically incriminated in the etiology of muscle cramps. Maybe I'd better take a second look at the regular V8 juice now more attractive because of its salt content. Perhaps it's all a conspiracy by mainstream medicine (via their low salt dogma) to generate business.

PC

No, just a guinea pig in a hula skirt, but I couldn't find any references to pigs and salt.

Richard

Here is a seawater analysis breakdown. Could our own bodies be similar in the ratios of minerals? Sodium is much higher than potassium, as is magnesium compared to calcium, and chloride is the highest. Is the amniotic fluid like the ocean? I'll have to see what I can find on that.

http://www.cea-life.com/SeawaterAnalysisTable.pdf

Richard

Richard,

You raise a very good point. The seawater connection has been underscored by many medical researchers wrt aldosterone in particular. Please visit

http://www.medscape.com/viewarticle/422919_8?WebLogicSession=P1yN1k1m9vw7ZU6f9GytaSGT7v2dRuJ6rWYhiy7BWmiPgw52EXRu|-4574489889599287599/184161395/6/7001/7001/7002/7002/7001/-1

On another note, my record run has come to an end. Last night while I slept AF reared its ugly head. The good part is that I think it was because I got behind in my hydration yesterday. The weather in SoCal has been very hot and unseasonably humid. I walked 18 holes in the AM, ran 5 miles in the afternoon and was on my feet most of the day. Even though I took in about 2 liters, I was aware of being behind the eight-ball. Additionally my urinary output was well below the usual. Since I'd started taking vitamins and supplements again, urine was yellow anyway, further camouflaging the emerging dehydration. So it's not back to the drawing boards, it's just being more careful. Also I plan to stop the vits and supps since they don't seem to offer much for my LAF, although they are justifiably recommended for general health.

PC, the guinea pig in search of salt

PC,

You were one busy guy, playing 18 and doing 5 miles. I hate to hear that your record was broken, but I agree, that all is not lost, and feel that hydration may very well be a key ingredient. I read your link, and was amazed at the devastation that aldosterone does cause. I really had no idea. I will continue drinking my water, as Dr. PC prescribes, and hope in the near future that I can eliminate the flec. I'm still on a search for the contents of the amniotic fluid, as I would think that closely represents perfection in the balance of the fluid content of the body. Maybe seawater does represent that balance, as well. It would be interesting to compare the two. Thank you for the link and all you do here, as I have learned much from you, even amidst all the brain cramps.

Richard

Thanks for taking the time and giving your opinion. I will certainly check out the questions you raise and come back with them. The only thing I know about glutamate receptors are there are two kinds - and more glutamate receptors are being discovered in many more areas of the body annually. I am not sure if they are only found in neural tissue. Is the pancreas neural?

On the salt note, as I was growing up I used to get terrible leg cramps. My grandmother (a rural Welsh Mountain Midwife in the 1920's and 30's) told me that cramps were due to a deficiency in salt. I often think there is a lot more to 'old wives tales' than meets the eye. Also the standard dehydration recipe given is a mixture of water, salt and sugar made to taste like tears. This supposedly rebalances the electrolytes. I can attest to water on its own after sunstroke can make matters worse.

All farm animals are given salt licks if they have no access to the shore here. It is recognised that salt is an integral part of their diet and can give rise to many ailments if not met.

Fran

Sorry to bombard you. l suppose I am working this out on line, but I know it is implicated more than is realised. And I am determined to find the answer.

Something about glutamate transporters... as opposed to glutamate receptors

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?holding=npg&cmd=Retrieve&db=PubMed&list_uids=11369436&dopt=Abstract

Department of Anatomy, Institute of Basic Medical Sciences, University of Oslo, P.O. Box 1105, Blindern, N-0317, Oslo, Norway.

Brain tissue has a remarkable ability to accumulate glutamate. This ability is due to glutamate transporter proteins present in the plasma membranes of both glial cells and neurons. The transporter proteins represent the only (significant) mechanism for removal of glutamate from the extracellular fluid and their importance for the long-term maintenance of low and non-toxic concentrations of glutamate is now well documented. In addition to this simple, but essential glutamate removal role, the glutamate transporters appear to have more sophisticated functions in the modulation of neurotransmission. They may modify the time course of synaptic events, the extent and pattern of activation and desensitization of receptors outside the synaptic cleft and at neighboring synapses (intersynaptic cross-talk). Further, the glutamate transporters provide glutamate for synthesis of e.g. GABA, glutathione and protein, and for energy production. They also play roles in peripheral organs and tissues (e.g. bone, heart, intestine, kidneys, pancreas and placenta). Glutamate uptake appears to be modulated on virtually all possible levels, i.e. DNA transcription, mRNA splicing and degradation, protein synthesis and targeting, and actual amino acid transport activity and associated ion channel activities. A variety of soluble compounds (e.g. glutamate, cytokines and growth factors) influence glutamate transporter expression and activities. Neither the normal functioning of glutamatergic synapses nor the pathogenesis of major neurological diseases (e.g. cerebral ischemia, hypoglycemia, amyotrophic lateral sclerosis, Alzheimer's disease, traumatic brain injury, epilepsy and schizophrenia) as well as non-neurological diseases (e.g. osteoporosis) can be properly understood unless more is learned about these transporter proteins. Like glutamate itself, glutamate transporters are somehow involved in almost all aspects of normal and abnormal brain activity.

Publication Types:
Review
Review, Academic

PMID: 11369436 [PubMed - indexed for MEDLINE]

I am not very good on physiology. But if the heart has presynaptic and synaptic cells (and I assume it does) then glutamate will directly open calcium and sodium channels. The following article says that the regional distribution for glutamate is everywhere.

http://www.psychology.psych.ndsu.nodak.edu/mccourt/website/htdocs/HomePage/Psy486/Biochemistry%20and%20Neuropharmacology/synaptic%20transmission%20and%20neuropharmacology.htm

(Richard, you will like this site, maybe you posted it before)

Glutamate

Biosynthesis: Synthesized from glutamine

Receptors: Mediating channels of three types: Quisqualate, Kainate and NMDA. NMDA receptor allows Na+ and Ca2+ influx. Excitotoxicity of Kanic acid (and CO & NO) via Ca2+.

(1) synthesis of glutamate (GLU) from glutamine; (2) transport and storage; (3) release of GLU by exocytosis or from cytosol; (4) binding of GLU to several types of receptors identified by specific antagonists [N-methyl-D-aspartate (NMDA), kainate (K), quisqualate (Q)]. The Q and K receptors gate Na+ and K+ flux; the NMDA receptor regulates a Ca2+-permeable conductance state which is normally blocked by Mg2+ and high resting membrane potential (-); when this block is relieved by membrane depolarization (+), Ca2+ flows in to depolarize the membrane further and activate other second messenger systems. The three receptor mechanisms illustrated in the figure represent different conductance states of the same receptor-channel complex.? (5) binding to presynaptic receptors; (6) reuptake; (7) degradation. A similar sequence is involved at synapses utilizing aspartate.

Regional Distribution: everywhere

Physiological Functions: workhorse excitatory transmitter. Mediates excitotoxicity -- mention ALS and hypoxic ischemia; PCP is therapeutic. Appears to play a role in learning and memory. MSG (monosodium glutamate), a preservative found in many oriental foods, activates some glutamic acid receptors and may cause dizziness and numbness.

From http://www.brainmachines.com/body_neurotransmitters.html

"Neurotransmitters are chemicals made by neurons and used by them to transmit signals to the other neurons or non-neuronal cells (e.g., skeletal muscle; myocardium, pineal glandular cells) that they innervate. The neurotransmitters produce their effects by being released into synapses when their neuron of origin fires (i.e., becomes depolarized) and then attaching to receptors in the membrane of the post-synaptic cells. This causes changes in the fluxes of particular ions across that membrane, making cells more likely to become depolarized, if the neurotransmitter happens to be excitatory, or less likely if it is inhibitory. "

From this I conclude that there does not need to be a glutamate receptor in the heart muscle, although I am sure there will turn out to be one. And as is known ingestion of free glutamate affects the body 20 times more than bound glutamate. Taken that free glutamate is added or made inadvertently in the processing of most commercial foods, pills and supplements and most people consume them on more than a daily basis, the balance is gone and the body cannot keep up.

It has been shown that more than one neurotransmitter can work on a specific receptor and there is cross talk between synapses with further reaching conclusions.

As glutamate interferes with K and Na I still wonder what its effects are on aldosterone. It might induce it further, especially in view of the above article "ABSTRACT: Objectives: a) To study the effect of S-allyl cysteine sulphoxide (SACS) on histological and ultrastructural changes in liver, kidney, heart and brain produced by monosodium glutamate (MSG) in rats on atherogenic diet".

Hope I haven't strayed too much from the main topic.

Fran

Fran,

It is my understanding that glutamate the neurotransmitter is not found outside the CNS (central nervous system). Glutamate is certainly found outside the CNS but it does not function as a neurotransmitter elsewhere. In short it is not

a neurotransmitter for peripheral nerves. The neurotransmitter for the vagus nerve in the heart is acetylcholine. Anything outside the CNS (brain and spinal cord), whether autonomic (involuntary) or voluntary is considered peripheral.

Fran, this is my understanding of glutamate and it is for this reason that I don't think you're going to find anything linking glutamate to receptors in the heart. Furthermore, if glutamate receptors were hypothetically placed on intracardiac peripheral nerves, this doesn't mean that the cardiac muscle fibers respond directly to them, i.e., opening and closing of various ion channels in the muscle cells, etc. Nerves and muscles both have their own receptors for these channels. They act similarly (much faster in nerves) with propagation of an impulse.

Just my recollection of the physiology. I know you'll take this as a challenge, so keep me informed.

PC

Fran,

I read your link, and you were right; I did like it. Even saved it to favorites. It gave me visuals that I had not had before. I take it that you use salt. What kind of salt do you use?

Thank you,
Richard

I found this site to be very interesting. I have copied just a portion. So maybe sodium is more important than we thought.

Potassium

Potassium directly increases aldosterone secretion by the adrenal cortex and aldosterone then lowers serum potassium by stimulating its excretion by the kidney. High dietary potassium intake increases plasma aldosterone and enhances the aldosterone response to a subsequent potassium or angiotensin II infusion (11). The primary action of potassium for stimulating aldosterone secretion is to depolarize the plasma membrane, which activates voltage-dependent calcium channels, that permit influx or exflux of extracellular calcium (11). The increased cytosolic calcium stimulates the same two steps in aldosterone biosynthesis that angiotensin II does (13).

Pituitary Factors

ACTH and possibly other POMC-derived peptides, including a-MSH, a-MSH, b-LPH and b-END, influence aldosterone secretion, however, the role of ACTH in aldosterone secretion is minor (10). ACTH increases aldosterone secretion by binding to glomerulosa cell-surface melanocortin-2 receptor, by activating adenylate cyclase, and increasing intracellular cAMP (15). Like other agents, ACTH stimulates the same two early and late steps of aldosterone biosynthesis.

Vasopressin has a modest and transient stimulatory effect on aldosterone secretion from zona granulosa cells in vitro. This effect is probably mediated via V2 receptors and phospholipase C generating IP3 and diacylglycerol (16).

Sodium

Sodium intake influences aldosterone secretion by an indirect effect through renin and to a minor extent by direct effects on zona glomerulosa responsiveness to angiotensin II. High sodium intake increases vascular volume, which suppresses renin secretion and angiotensin II generation and decreases the sensitivity of aldosterone response to angiotensin II (17).

Inhibitory agents

Dopamine inhibits aldosterone secretion in humans by a mechanism that is independent of the effects of prolactin, ACTH, electrolytes and the renin-angiotensin system (18). This inhibitory effect may involve binding to D2 receptors on glomerulosa cells (19). Atrial natriuretic peptide (ANP) directly inhibits aldosterone secretion and blocks the stimulatory effects of angiotensin II, potassium and ACTH, at least in part, by interfering with extracellular calcium influx (20).

MECHANISMS OF ALDOSTERONE ACTION

Effect of Aldosterone
Aldosterone is crucial for sodium conservation in the kidney, salivary glands, sweat glands and colon. Aldosterone promotes active sodium transport and excretion of potassium in its major target tissues. It exerts its effects via the mineralocorticoid receptor (MR) and the resultant activation of specific amiloride-sensitive sodium channels (ENaC) and the Na-K ATP ase pump (21). Aldosterone and the MR may be involved in the regulation of genes coding for the subunits of the amiloride sensitive sodium channel and the Na-K ATP ase pump, as well as of other proteins (22,23). Aldosterone indeed increases the number of active sodium channels and augments the action and number of the Na-K ATP ase pump units in its target tissues (24).

Defective Stimulation of Aldosterone
The first category of conditions, which is characterized by defective stimulation of aldosterone secretion, includes the syndromes of congenital and acquired hyporeninemic hypoaldosteronism. One of these conditions is due to a defect of renin secretion such as hyporeninemia resulting from b-blockers, prostaglandin synthetase inhibitors, and calcium channel blockers. Another condition is due to decrease in the conversion of angiotensin I to angiotensin II mediated by converting enzyme inhibitor medications and is associated with hyperreninemia.

Defective Aldosterone Actions
The third category which is characterized by defective aldosterone action includes syndromes of aldosterone resistance such as pseudohypoaldosteronism type 1 and sodium-wasting states resulting from excessive amounts of circulating mineralocorticoid antagonists, such as spironolactone and its analogues, and synthetic progestin or natural agonists, such as progesterone or 17-hydroxyprogesterone. These mineralocorticoid antagonists may antagonize aldosterone at the levels of mineralocorticoid receptor (54) and frequently, these states are compensated for by elevated concentrations of plasma aldosterone.

http://www.endotext.com/adrenal/adrenal24/adrenalframe24.htm

This is well worth reading, if it hasn't already been posted previously, and I missed it.

Richard

Hello Hans & Everyone,

I've been a little out of touch, and wasn't aware of this topic until today.

Recently I have upped my Mg glycinate to 800mg/day and it has made some difference. I haven't been hydrating as much as I probably should, and I have used very little salt in my diet for a long, long time. I would think the amount of salt one adds to water would vary according to salt intake with one's own diet. So I would think for one like me (very low salt intake) adding 1/4 teaspoon per liter just might be ok. This is all very interesting and makes good sense! Believe I will give it a try. Oh, how much water are we supposed to be drinking/day? I realize more if one is sweating due to exercise, etc.

Thanks,
Jim W.

Richard. The salt I use is naturally panned in the old tradition. The sea water is left to evaporate and the salt forms. As I do not eat any processed foods I do not worry about salt. My husband thinks I take very little, but I take what my body thinks is good. Sometimes I put a lot on, sometimes very little. It just depends on what I feel like.

PC

Its good to be challenged, otherwise things get stuck. Most of this research is very new.

My understanding is different. I may have missed something critical, but experience and research makes sense that the heart is involved too. At present I can't find anything with direct regard to the heart but.... I will keep chasing. Meanwhile it may not be the main neurotransmitter.. but it certainly has an impact outside the CNS.

What jumps out to me is the impact of glutamate on the epithelial cells. And these are present in the heart. so bearing this in mind, if you can b bothered... read on

There are glutamate receptors in THE PANCREAS

http://www.holistichealth.com/new_page_4.htm
In addition to the brain, the other area of the body that is able to concentrate the excitotoxin glutamate is the pancreas, which would result in further damage to the pancreas and sugar regulation.

http://health.ucsd.edu/news/2003/06_11_Reddy.html
"As reported in the June 12, 2003 issue of the journal Nature, severe cases of cystic fibrosis are caused when epithelial cells of sweat glands, intestine, lung and pancreas are unable to transport bicarbonate (which also serves as a buffer between acidity and alkalinity in the blood) across their cell membranes.

In addition, the researchers found that glutamate, an amino acid best known as a brain neurotransmitter, controls the movement of bicarbonate and another important chemical, chloride, into and out of epithelial cells. The two appear to act independently, but it is generally believed that their movement across cell membranes brings water to mucus that protects the cells, thus keeping the tissues lubricated and the mucus from becoming sticky and thick. However, scientists also believe that the contribution of these two chemicals to normal health is much more complex.....

We focused on glutamate because of its predominant role in regulating the neuronal channels and because glutamate receptors are widely distributed in epithelial cells*, even though the functional significance of these receptors is almost unknown," said M.M. Reddy, Ph.D., the study's primary author and a research scientist in the UCSD Department of Pediatrics."

* epithelium - The covering of internal and external surfaces of the body, including the lining of vessels and other small cavities. It consists of cells joined by small amounts of cementing substances. Epithelium is classified into types on the basis of the number of layers deep and the shape of the superficial cells.

THE RETINA
http://www.med.wayne.edu/anatomy/department/pourcho.htm
Major Research Interests
Cytochemical and biochemical studies of retinal neurotransmitters and their receptors. Analysis of synaptic relationships of transmitter-specific neurons in the retina.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?holding=npg&cmd=Retrieve&db=PubMed&list_uids=9667006&dopt=Abstract
"The main neurotransmitters in the vertebrate retina are glutamate, GABA and glycine. Their localization in the different cell types in the retina is well known. In addition, there exists a number of neuropeptides and other neuroactive substances that are only expressed by sparse populations of neurons. In recent years, molecular biology has led to the discovery of a rapidly increasing number of neurotransmitter receptors and the apparent simplicity of neurotransmitters in the mammalian retina is contrasted by the expression of a plethora of neurotransmitter receptors and receptor subunits (not mentioning receptor isoforms). This article will concentrate on glutamate receptors with the intention of reviewing some of the recent data on glutamate receptor expression in the mammalian retina and their possible involvement in retinal function".

THE HAIR CELLS OF THE EAR (vertigo, menieres, tinatus etc)
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?holding=npg&cmd=Retrieve&db=PubMed&list_uids=9481795&dopt=Abstract
"Ottersen OP, Takumi Y, Matsubara A, Landsend AS, Laake JH, Usami S.

Department of Anatomy, Institute of Basic Medical Sciences, Oslo, Norway.

The synapses between sensory cells in the inner ear and the afferent dendrites of ganglion cells are well suited to investigations of fundamental mechanisms of fast synaptic signalling. The presynaptic elements can be isolated for electrophysiological and functional studies while the synapses can be easily recognized in the electron microscope due to their distinct morphological features. This allows for a broader range of correlative functional and structural analyses than can be applied to synapses in the central nervous system (CNS). As in most fast excitatory synapses in the CNS the transmitter in the afferent hair cell synapses appears to be glutamate or a closely related compound. Recent studies have revealed many of the key molecular players at this type of synapse and how they are spatially and functionally coupled. By use of high resolution immunogold cytochemistry it has been shown that AMPA glutamate receptors are specifically expressed in the postsynaptic specialization of afferent hair cell synapses (except at those established by outer hair cells in the organ of Corti) and that their density varies as a function of the distance from the release sites (demonstrated for the afferent contacts of inner hair cells). The glutamate transporter GLAST is localized in supporting cell membranes and concentrated in those membrane domains that face the synaptic regions. Glutamine synthetase and phosphate-activated glutaminase--which are responsible for the interconversion of glutamate and glutamine--are selectively localized in non-neuronal and neuronal elements, respectively. Taken together with quantitative immunogold data on the cellular compartmentation of glutamate and glutamine the above findings suggest that the sensory epithelia in the inner ear sustain a cycling of glutamate carbon skeletons. In this process, the supporting cells may carry out functions analogous to those of glial cells in the CNS. Functional and morphological analyses of the presynaptic membrane indicate that L-type Ca(2+)-channels and Ca(2+)-activated K(+)-channels are colocalized and clustered at the active zone. Influx through the L-type channels triggers synaptic release and their close spatial association with Ca(2+)-activated K(+)-channels appears to be critical for frequency tuning. The focal expression of different Ca(2+)-channels combined with a high intracellular buffering capacity permits several Ca(2+)-signalling pathways to operate in parallel without undue interference. The molecular organization of the afferent hair cell synapses reflects the functional demand for speed and precision and attests to the ability of the pre- and postsynaptic elements to target and anchor key proteins at specific membrane domains."

and http://www.unizh.ch/orl/politzer/abst/d03.htm

THE LUNGS
http://ajrcmb.atsjournals.org/cgi/content/abstract/2003-0177OC
Submitted on May 6, 2003
Revised on July 8, 2003

Ionotropic glutamate receptors in lungs and airways: molecular basis for glutamate toxicity
Kathleen G Dickman1, J. Georges Youssef2, Suni M Mathew3, and Sami I Said1*
1 VA Medical Center, Northport, N.Y., USA; Medicine, SUNY at Stony Brook, Stony Brook, N.Y., USA, 2 Medicine, SUNY at Stony Brook, Stony Brook, N.Y., USA, 3 VA Medical Center, Northport, N.Y., USA

We earlier showed that the ionotropic glutamate receptor agonist NMDA induces excitotoxic pulmonary edema, and that endogenous activation of NMDA receptors (NMDAR) could mediate lung injury caused by oxidative stress. In this study, we searched for evidence of NMDAR expression in the rat lung and in the alveolar macrophage (AM) cell line NR8383, and for possible regulation of receptor expression by NMDA. The presence of mRNA for NMDAR 1 and the 4 known NMDAR 2 subtypes (A, B, C, and D) was examined by RT-PCR using isoform-specific primers. NMDAR 1 was expressed in all lung regions examined (peripheral, mid-lung, and mainstem), as well as in trachea and the AMs. Expression of NMDAR 2A and 2B subtypes was not detected, while NMDAR 2C was present only in peripheral and mid-lung samples. NMDAR 2D was the dominant subtype expressed in the peripheral, gas-exchange zone of lung and in alveolar macrophages, and this expression was upregulated in lungs treated with NMDA. Western blot confirmed the presence of NMDAR 1 protein in all lung regions and in AMs. These findings provide a molecular-biological basis for the excitotoxic actions of glutamate in rat lungs and airways, and raise the question of a possible physiological role for

NMDA receptors in lung and airway function.

http://www.smallbore.20m.com/smallbore_rifle/mental_and_physical.html

http://www.truthinlabeling.org/scripps-1.html
On August 31, 1995, the Food and Drug Administration (FDA) released a report on the safety of MSG in food, done by the Federation of American Societies for Experimental Biology (FASEB). In that report, FASEB acknowledged that MSG had an effect on some asthmatics, and that doses of MSG as low as .5 grams MSG had been known to trigger MSG reactions.

http://www.jcb.org/cgi/content/full/162/1/13-a
Research Roundup
Glutamate in unusual places

Published online June 30, 2003 as 10.1083/jcb1621rr4.

Mild CFTR mutations mainly affect Cl- transport (left), but severe forms also perturb bicarbonate conductance (right). Reddy/Macmillan

Glutamate has a critical physiological function unrelated to its job as a neurotransmitter, according to results from M. M. Reddy and Paul Quinton (University of California, San Diego, CA). The duo find that glutamate activates an epithelial ion channel that is mutated in patients with cystic fibrosis. ...

Cl- may not be the only CFTR-conducted ion important for normal gland function. Reddy found that bicarbonate ions also passed through the CFTR channel in the presence of both glutamate and ATP. Mutant versions of CFTR found in patients with severe forms of cystic fibrosis were deficient in both Cl- and bicarbonate transport. Milder CFTR mutations spared bicarbonate transport. The findings suggest that defects in bicarbonate transport should not be ignored in the search for treatments for cystic fibrosis.

Reference:
Reddy, M., and P. Quinton. 2003. Nature. 423:756–760.[CrossRef][Medline]

Fran

Yeah (I hope I haven't miss read this) - I found something that links NMDA receptors (glutamate) to the heart and vagal activity. And also mentions G proteins and aldosterone.... I'm sure there is a way to go yet. But now I am convinced that I am on the right track. But boy it is complicated and complex.

http://nips.physiology.org/cgi/content/full/14/4/155

Synaptic inputs to cardiac vagal neurons include NTS neurons, which activate both NMDA and non-NMDA receptors in cardiac vagal neurons. It is also likely that postinspiratory cholinergic neurons activate postsynaptic nicotinic receptors and directly excite these neurons, which may be a mechanism responsible for respiratory sinus arrhythmia. Postinspiratory cholinergic neurons also likely activate presynaptic nicotinic receptors on glutamatergic terminals, which could facilitate, or gate, the baroreflex during postinspiration. However, much work is still needed, especially investigations concerning the presynaptic and postsynaptic receptors activated upon stimulation of identified synaptic pathways to cardiac vagal neurons and alterations in these receptors and channels during pathological disease states. It is hoped that a further understanding of the functional importance and pharmacological properties of presynaptic and postsynaptic receptors that determine cardiac vagal activity in the brain stem may allow us to identify agents that can reduce cardiac vagal activity in pathological conditions with abnormally low heart rates and cardiac function, such as SIDS, as well as increase vagal cardiac activity and reduce the fatality associated with cardiac hyperexcitability.

Also we have mention of the role of glutamate receptors in the periphery and the role of pain (opoids).

http://opioids.com/tolerance/glutamate.html

Glutamate and glutamate receptors are located in areas of the brain, spinal cord and periphery that are involved in pain sensation and transmission. Glutamate acts at several types of receptors, including ionotropic (directly coupled to ion channels) and metabotropic (directly coupled to intracellular second messengers). Ionotropic receptors include those selectively activated by N-methyl-D-aspartate, alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate. Metabotropic glutamate receptors are classified into 3 groups based on sequence homology, signal transduction mechanisms and receptor pharmacology. Glutamate also interacts with the opioid system, and intrathecal or systemic coadministration of glutamate receptor antagonists with opioids may enhance analgesia while reducing the development of opioid tolerance and dependence.

Exhausted and read out.

Fran

Fran,

I have no doubt that "glutamate has a critical physiological function unrelated to its job as a neurotransmitter".

Glutamate receptors may be widely distributed in epithelial cells (in which case it is not functioning as a neurotransmitter). However, I tend to doubt the accuracy of any article that additionally states that epithelial cells line blood vessels and small cavities. Endothelial cells line the inside of blood vessels and mesothelial cells line the inside surfaces of body cavities. I look at them everyday under the microscope. That article appears to have been written by a layperson who probably mistook endo and meso for epi. Accordingly there are no epithelial cells in the heart or blood vessels.

The rest of the article is far to technical and probably inaccurate to tackle. The others are research articles that, like many quoted on this BB, are full of technical research minutiae with very little discernible clinical application.

PC

Epithelium - The covering of internal and external surfaces of the body, including the lining of vessels and other small cavities. It consists of cells joined by small amounts of cementing substances. Epithelium is classified into types on the basis of the number of layers deep and the shape of the superficial cells.

This quote came from an online dictionary, which I looked up as I had never heard of them before. I added it in case anyone else didn't know what they were. The quote didn't come from the research articles. Thanks for enlightening me.

But your question was "If you find that glutamate is a Ca or Na channel opener in the heart, please let me know"

The last article I published shows that it is. http://nips.physiology.org/cgi/content/full/14/4/155

Fran

Richard
I came across something called G Proteins tonight and wondered how they might affect aldosterone. Could this be the underlying factor that predisposes us to AF...?

http://www.washington.edu/alumni/columns/june96/rodbell_sidebar.html

"the Nobel-prize winning work of Martin Rodbell proved that there is a lot more going on--a series of switches have to be thrown chemically in order for the message to get passed along. A key to those chemical switches are G proteins.

And if something is wrong with this process, such as leaving the switch "on" or "off" for too long, there is trouble.

Scientists now know that cholera alters the G proteins, leaving the switch "on" for too long, which prevents the normal absorption of salt and water in the intestines--leading to dehydration or even death.

Diabetes and alcoholism are thought to be caused, in part, by G protein malfunction, and scientists have also traced a form of pituitary cancer to impaired G proteins. While G protein research has not yet let to a miracle cure, the discovery may lead to eventual treatments."

The fact the two are connected can be shown here

http://ajpcell.physiology.org/cgi/content/abstract/268/3/C557

Aldosterone stimulation of GTP hydrolysis in membranes from renal epithelia
S. Sariban-Sohraby, F. Mies, M. Abramow and R. S. Fisher
Laboratoire de Physiopathologie, Universite Libre de Bruxelles, Belgium.

Specific hydrolysis of GTP catalyzed by membranes prepared from A6 epithelial cells grown on porous supports was measured. Aldosterone treatment of the cells for 4 h increased Na+ transport and stimulated GTP hydrolysis by apical membranes in vitro more than twofold over basal levels. This stimulation was attributed to an increase in maximum velocity with little change in Michaelis-Menten constant values. Na+ transport rate and GTP hydrolysis were linearly correlated after aldosterone. This relationship was maintained when aldosterone's response was blunted by various inhibitors. Spironolactone decreased both the hormone-stimulated guanosinetriphosphatase (GTPase) and the Na+ transport rate. Pertussis toxin, which exerted minimal effects on basal rates, reduced the increase of Na+ current normally observed after aldosterone and the hormone stimulation of GTPase activity. The expression of classical Gi/Go-type G proteins was not increased after hormone treatment. When A6 cells were grown on nonporous plastic dishes, aldosterone neither stimulated GTPase activity nor increased amiloride-blockable 22Na+ fluxes. We propose that activation of one or more G proteins in the apical membrane of A6 cells is directly involved in the natriferic action of aldosterone".

And here are the epithelial cells again which are also targetted by glutamate..... Forgive me for this seemingly unconnected bombardment to a connection with aldosterone and free glutamate again. But somewhere along the line I know it is all tied up. Just wish I had the wits to put it together in a better format.

Anyway http://www.xagena.it/einthoven/eint0041.htm

6. Autonomic control mechanisms

One of the factors that influence arrhythmias is autonomic control.

Receptor systems are linked to their effectors via a complex series of steps.
At the simplest level, these may involve "G proteins". These are guanidine triphosphate regulatory proteins that transduce a signal generated by receptor activation. G proteins have three subunits: beta and gamma, which are membrane bound, and alpha, which can, under certain circumstances, become unbound from the beta and gamma subunits. When the agonist binds to the receptor, the alpha subunits is unbound and free to interact with a variety of systems (second messengers, channels and pumps) giving rise to an effector response.

AND

http://nips.physiology.org/cgi/content/full/14/4/155

From this site I have just found that Glutamate does directly affect the heart. Allbeit recommending it for low vagal tone..... HA ha

One possibility is that there are cholinergic neurons active in postinspiration that project to cardiac vagal neurons. These neurons could influence cardiac vagal neurons via three independent mechanisms. One site of action would be via a direct activation of postsynaptic ligand-gated nicotinic channels in cardiac vagal neurons, which would act to depolarize and excite cardiac vagal neurons during postinspiration. An additional site of action would be presynaptic

and would evoke a nicotinic facilitation of presynaptic release of glutamate. A third action of the postinspiratory neurons would be to augment glutamatergic neurotransmission by activating nicotinic receptors that facilitate postsynaptic non-NMDA receptors in cardiac vagal neurons. These latter two effects could constitute mechanisms by which respiratory inputs gate, or facilitate, the baroreflex during postinspiration.
In summary, during the last 5 years there has been considerable progress in our understanding of the voltage-, Ca-, and ligand-gated channels, synaptic pathways, transmitters, and receptors involved in the central control of cardiac vagal activity. It is apparent that cardiac vagal neurons are inherently silent and depend on excitatory synaptic input for their activity. Synaptic inputs to cardiac vagal neurons include NTS neurons, which activate both NMDA and non-NMDA receptors in cardiac vagal neurons. It is also likely that postinspiratory cholinergic neurons activate postsynaptic nicotinic receptors and directly excite these neurons, which may be a mechanism responsible for respiratory sinus arrhythmia. Postinspiratory cholinergic neurons also likely activate presynaptic nicotinic receptors on glutamatergic terminals, which could facilitate, or gate, the baroreflex during postinspiration. However, much work is still needed, especially investigations concerning the presynaptic and postsynaptic receptors activated upon stimulation of identified synaptic pathways to cardiac vagal neurons and alterations in these receptors and channels during pathological disease states. It is hoped that a further understanding of the functional importance and pharmacological properties of presynaptic and postsynaptic receptors that determine cardiac vagal activity in the brain stem may allow us to identify agents that can reduce cardiac vagal activity in pathological conditions with abnormally low heart rates and cardiac function, such as SIDS, as well as increase vagal cardiac activity and reduce the fatality associated with cardiac hyperexcitability.

Fran

Fran,

The discussion you quoted linking glutamate directly to the heart from the lungs is not as it might seem. Look up presynaptic and postsynaptic neurons. Glutamate in that discussion is operating within the CNS. Stretch fibers in the lung upon inpiration send an impulse directly to the brainstem, where another neuron (with its axon in the vagus nerve) is inhibited via the neurotransmitter glutamate and this postsynaptic neuron then results in vagal withdrawal or less vagal tone. This, of course, causes the HR to increase during inspiration and is called respiratory vagal arrhythmia. There are other neural pathways which operate simultaneously and involve the caotid and aortic baroreceptors.

Always here to make a seemingly simple concept more complicated.

PC

Yes it is far too complicated. The more I try to understand the more I feel a fool. But I cannot give up. Thanks for helping. I'll forgive you if you just give up on me.

Are you saying

"Synaptic inputs to cardiac vagal neurons include NTS neurons, which activate both NMDA and non-NMDA receptors in cardiac vagal neurons"

means that the glutamate is working on the vagal nerve as a neurotransmitter in the CNS. The last line of this paper states:

"It is hoped that a further understanding of the functional importance and pharmacological properties of presynaptic and postsynaptic receptors that determine cardiac vagal activity in the brain stem may allow us to identify agents that can reduce cardiac vagal activity in pathological conditions with abnormally low heart rates and cardiac function, such as SIDS, as well as increase vagal cardiac activity and reduce the fatality associated with cardiac hyperexcitability."

Now just where are NMDA receptors in cardiac vagal neurons found. I had assumed the vagus nerve (in the ANS), which in a sense, must be regulated by the CNS to some exent if the above is correct. And will have a direct affect on heart rhythm.

This to me says Free Glutamate initiated LAF stems from the brain, and with your input from the CNS, not the ANS.

Now I know at this point it is looking like glutamate does not directly affect the heart muscle. But the fact that they use calcium channel blockers for AF, and glutamate is a calcium channel opener, it seems to me they should be looking to see if there are glutamate receptors in the heart. It was only recently they found them in the breast. No one will know until someone looks. I'm not asking you to answer this. It is part of what I started with - and am left with.

Fran

PS. I discover that cardiac vagal neurons are found in the "nucleus ambiguus (NA) and the dorsal motor nucleus of the vagus (DMNX)" Now to find a diagram

http://www.annalsnyas.org/cgi/content/abstract/940/1/237

Very good, Fran.

You now know more neuroanatomy than 99% of MDs. The nucleus ambiguus and the DMNX are the two arms of the vagus nerve about which I've posted in the past (see last years post on RSA=respiratory sinus arrhythmia and why swallowing can trigger AF). The former controls HRV (which we can control ourselves voluntarily to some extent by varying our breathing) and the latter controls heart period variability, i.e., slower rate at night and higher during the day independent of what we're doing.

The nucleus tractus solitarius (NTS) in the medulla oblongata (part of the brainstem) is the collection of ganglion cells that receive via their axons the messages from the stretch fibers in the lung and these then trigger the ganglion cells in the NA (via glutamate) which send signals from the medulla to the heart (as the vagus nerve). NTS are presynaptic and NA are postsynaptic. This is my understanding and I hope someone that knows more than I will speak up if this is incorrect.

Your comments about Ca channel blockers are very reasonable. The hooker is that Ca channel blockers are needed in any cell that sends signals or waves. It's an electrical phenomenon in both nerves and muscles that allows them to function as they do. However, only nerves have neurotransmitters. Then you get into the difference between a neurotransmitter (a kind of localized hormone) and a circulating hormone. Perhaps glutamate could do both.

I won't give up on you Fran so you can't forgive me.

PC

Hello All,

I think this in an excellent article and has many points that pertain to us, with just a few highlights, as follows:

Osmolality is influenced by changes in sodium concentration. For example, ingestion of salt raises plasma osmolality and stimulates the osmoreceptors to provoke thirst and reduce water excretion. This leads to an increase in total body water which reduces salt concentration and osmolality. Thus it is the intake and loss of water rather than changes in sodium that determine plasma osmolality. Water is, therefore, vital for controlling plasma sodium concentration. iv Conversely, body volume (total body water) is controlled by altering body sodium concentration because sodium is the major extracellular osmole. There are no sensors that can detect effective circulating volume. However, since volume and pressure are directly related, the body measures pressure changes in the form of vascular stretch (the fullness of the blood vessels) at various sites and uses this to monitor the effective circulating volume.

Arterial blood pressure is monitored by baroreceptors in the carotid sinus and aortic arch. Stretch receptors in the right atrium of the heart monitor venous pressure and fluctuations in kidney perfusion are monitored by stretch receptors in

the renal afferent arteriole. Signals from these stretch receptors trigger cardiovascular and renal responses. For example, if body volume is too low (hypovolaemia), the level of the hormone aldosterone is increased which causes renal sodium reabsorption.

8.3 Cardiovascular disease
The mechanical function of the heart may be related to cell volume. Since cells shrink when dehydrated, this may alter the distances between cardiac cells and these distances are important in the contraction of heart muscle. In addition cellular volume changes may interfere with the contraction of heart muscle via changes in intracellular calcium.

12. Sport and exercise
Heat is produced during exercise and evaporation of sweat is the most effective method of cooling the body. (Heat energy is used to convert water into water vapour as sweat evaporates and this heat is taken from the skin, hence cooling the skin – it is called the latent heat of evaporation). Environmental conditions influence fluid losses, eg fluid loss is increased under conditions of excessive heat or cold, low humidity or high altitude.
Sweating rates of 1-2 litres per hour are typical during moderately hard exercise, but may be as high as 2 litres per hour in high ambient temperatures. xix The effects of dehydration can be particularly detrimental to athletes. If a 150 lb athlete loses 2% of his or her body weight (3 lb), physical and mental performance will decrease by 20%.xliv,xlv Chronic mild dehydration (1-2% loss of body weight) negatively affects athletic performance.xix Even at modest (<2%) levels, dehydration reduces aerobic endurance and results in increased body temperatures, heart rate, perceived exertion and possibly increased reliance on carbohydrate as a fuel source. These negative effects are exacerbated when the exercise is performed in a hot environment.xlvi At 2-3% loss of body weight, the reduction in plasma volume places a significant strain on circulatory function, which ultimately impairs the capacity for both exercise and thermoregulation (body temperature control).

This is all I'll post for now, but it sure seems that water is correlating to a lot of our issues that we have discussed in the past. There is a lot more to read than just this.

http://www.rsph.org/water/water%20and%20health.pdf

Richard

Fran,

I haven't done much reading on G proteins, so don't know much about them. I'm becoming more and more convinced of hydration being a big part of our problem. You've really been researching lately, and I appreciate all your posts. I hope you find the connection of glutamate to aldosterone. I'll keep that in mind when doing my own research. You've definitely peaked my curiosity.

Carol,

I'm not nearly as scientific minded as PC, so would have a hard time trying to put it into words, but basically hydration and sodium keep aldosterone at bay, but we still have to keep potassium in balance. If you read PC's past posts, he has explained it much more simply. I'm personally not going to focus too much on balancing, rather I'm going to make sure I eat plenty of potassium rich foods, and continue to salt, as I have been doing. The only difference I will be making is to drink a lot more water. I have not been a big water drinker, except when I was exercising, but that probably wasn't near enough. I only hope I can rectify the problem in doing the above. I am eating Paleo with organic meats, eggs, fish and lots of veggies and some fruits, and nuts, and of course some fats from meats, olive oil and grape seed oil. I wish I could help you more on the aldosterone issue, but that hasn't been my main course of study here, so I'm still learning, too.

Richard

I have a question:

I had blood work and a 24 hr. urine test done this past April, my aldosterone tested 2.0 ug/24 hrs, with lab values of a random sodium diet 2.3-21.0 ug/24 hours. Looks like my aldosterone is quite low yet I got and get afib every two weeks except for the month of Aug. when I went 30 days afib-free. My 17-oh-corticosteroids were on the high end, so for me it looks like high cortisol might be the bad guy not aldosterone or is this being too simplistic.

On July 31 I had a IV of Mag. and other minerals from a Holistic MD, no afib for 30 days. I am going next Monday and try another IV of Mag. to see what happens, my mag. tests on the low end, but, I am having a hard time taking more than 400 mgs. of mag. tabs, if the IV is working, I could have it done every month for a while to see what happens. It just costs a whole lot more than the mag. tabs.

P.C.
I know you were taking Spironolactone, I read that "Spironolactone significantly reduced heart rate (prolonged RR interval) particularly during the dawn hours", knowing that you are Vagal, that doesn't seem to bode well for you.

Liz

Liz,

I'm so glad you asked this question. I'll have to try to find and understand more on cortisol. My cortisol levels were on the high side, as well, and although Jerry emphasized the importance of this test, I guess I never really understood what to do, if they were high. Did you doctor explain what to do about it?

Liz, you might try the Waller Water, rather than supplements, as I was reading that Mg. in its ionic form is much more absorbable than supplements. David S. posted the recipe on the BB and it's easy to make.

I'll post what I find, but I'm going to ask Jerry, what he can share, too.

Richard

Liz,

Thanks for the info.

Hans also has questioned the value of an aldosterone blocker in that this should raise blood K a bit, which in turn should stimulate the production of more aldosterone, kind of like a dog chasing his own tail.

Also, it would be nice to know exactly what was meant by "the dawn hours". At daylight the normal circadian rhythm of vagal tone has dictated a considerable retreat from its night time tone. Perhaps it all boils down to whether you think aldosterone is involved in LAF and, if so, whether the mechanism of action is intracellular K imbalance or cardiac inflammation.

PC

In case anyone is interested I have just discovered that there are more than two glutamate type receptors. Here is a great site. Way over my head at the moment. Although I am sure the answer can be found here once I understand some of the terminology.

http://www.bris.ac.uk/synaptic/info/glutamate.html

This abstract does not mention calcium, but shows the effect of free glutamate direct on NA and K in the hearts of rats. Could only access it through cached.

http://216.239.41.104/search?q=cache:W0WRsLBLuO0J:medind.nic.in/imvw/imvw6609.html+effect+of+MSG+on+the+heart&hl=en&ie=UTF-8

Indian Journal of Pharmacology. 1999 Aug; 31(4): 266-74

ABSTRACT: Objectives: a) To study the effect of S-allyl cysteine sulphoxide (SACS) on histological and ultrastructural changes in liver, kidney, heart and brain produced by monosodium glutamate (MSG) in rats on atherogenic diet. b) To understand some cellular effects of MSG at higher dose in renal and hepatic tissues of rats of atherogenic diet. Methods: Rats on atherogenic diet with MSG at two different doses received SACS for 30 days. At the end of 30 days, NA+, K+ -ATPase, 5'nucleotidase and membrane fluidisation assays were carried out in heart, kidney, liver and brain, respectively. Histological observation was also carried out for liver and kidney. Results: SACS significantly decreased the Na+, K+ -ATPase and 5'nucleotidase activities in liver, kidney and heart in rats treated with MSG at both doses. There was no significant effect of SACS on brain Na+, K+ -ATPase and 5'nucleotidase in rats treated with both doses. Further, SACS significantly increased membrane fluidisation pattern in liver ,kidney, and heart in rats treated with MSG at both doses. MSG at higher dose produced sequence of damage in cellular organelles and membranes in renal and hepatic tissues. There was no significant effect of SACS on architectural, ultrastructural and histological changes induced by MSG in rats on atherogenic diet. Conclusion: SACS significantly antagonised the reversible damage produced by MSG in rats on atherogenic diet by modulating Na+, K+ -ATPase, 5' nucleotidase and membrane fluidisation process. Irreversible damage (oxidative stress) caused by MSG at higher dose on cell membrane and cell organelles of hepatic and renal tissues is not reverted by SACS in rats on atherogenic diet.
KEYWORDS:
Sodium Glutamate/AD; Lipid Peroxidation; Hyperlipidemia/DT; Cysteine; Amino Acids; Na(plus)-K(plus)- Exchanging ATPase; 5'-Nucleotidase; Oxidative Stress; Analysis of Variance; Rats; Data Interpretation, Statistical; Animal
References: 28
Record Identifier: NI210375

Other sites

http://ajpheart.physiology.org/cgi/content/full/275/5/H1567

Still nothing tying it with aldosterone but I am sure something will crop up. Gut feeling

Fran

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http://jneurochem.highwire.org/cgi/content/full/75/6/2472

This report has found a " Transient Expression of NMDA Receptor Subunit NR2B in the Developing Rat Heart".

With use of RT-PCR and western blot analysis, the expression of NMDA receptor subunit NR2B was investigated in the developing rat heart. NR2B mRNA and protein were detected in heart tissue of rats from embryonic day 14 until postnatal day 21 but disappeared 10 weeks after birth.

However, the NMDA receptor-specific antagonist MK-801 has been reported to exhibit a positive ionotropic action in adult rat heart, suggesting a modulation of K+, Na+, and Ca2+ channels (Huang and Su, 1999).

So this shows that glutamate could have a direct impact on the calcium and sodium channels of the heart? Oh for more like this...

Fran

And I missed this extract:

"Recently, the presence of several subunits of iGluRs and mGluRs in adult rat heart tissue was indicated by RNA and

protein techniques. Although Winter and Baker showed L-glutamate-induced changes in intracellular calcium oscillation frequency, the physiological function of glutamate receptors in the heart is not well understood."

BINGO. Unless I have misread it

Fran

PC

Dawn hours according to this article are 06:00-9:00., it is a short article and if you are interested, the link is http://isilinks.com:9000/gateway/CPL/cgi-bin/CPL.cgi?Func=FullRecord&PID=Highwire&U...

Liz

I couldn't access the link, here is the text:

Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients
MacFadyen, RJ;Barr, CS;Struthers, AD
CARDIOVASCULAR RESEARCH
35: (1) 30-34 JUL 1997

Document type: Article Language: English

Abstract:
Background: Experimental data suggest that aldosterone has harmful effects promoting myocardial fibrosis and disturbing autonomic balance. There has been no evidence of these potential effects in intact man. Methods and Results: We report the findings in 31 patients with stable chronic heart failure (CHF) who were treated with spironolactone (50-100 mg/day) or placebo in addition to diuretics and angiotensin converting enzyme (ACE) inhibition. In a controlled randomised double-blind study, we found that spironolactone treatment reduced circulating levels of procollagen type III N-terminal amino peptide, a marker of vascular collagen turnover, and in addition increased time-domain parameters of heart rate variability (n = 24). These latter parameters suggest a parasympathomimetic effect for additional spironolactone. Spironolactone significantly reduced heart rate (prolonged RR interval) particularly during the dawn hours (06.00-09.00 h). In this unbalanced study it was not possible to provide a detailed diurnal assessment of the impact of spironolactone on heart rate variability, but the preliminary data suggest that there may be an interaction with the autonomic nervous system which varies in time. Conclusions: These are the first human data to show that use of the aldosterone antagonist, spironolactone, can positively improve time-domain heart rate variability and reduce myocardial collagen turnover, as reflected by further reductions in serum procollagen peptide, despite concurrent ACE inhibitor treatment. Residual aldosterone after ACE inhibitor treatment may therefore have a role promoting arrhythmia and cardiac death by two mechanisms. Effects of additional spironolactone on slowing heart rate (and potentially the detrimental effect of aldosterone) were most prominent between 6 a.m. and 10 a.m. when cardiac death is also known to be most prominent.
Author Keywords:
ACE inhibitors, aldosterone, spironolactone, heart failure, sympathetic nervous system, heart rate, diurnal variation, collagen, human

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Liz

Thanks Liz.

That article was jointly authored by Dr. Struthers who wrote the section on the dangers of aldosterone wrt cardiac inflammation and fibrosis that has been oft quoted. I believe Hans has personally communicated with him.

Also, this parasympathetic effect of aldosterone blockade might not be presented in one without congestive heart failure.

PC

The author of this paper - Robert J MacFadyen now in Raigmore Inverness is none other than my ex cardiologist. He knows nothing about AF. He is the one that insisted my GP keep me on sotalol at all costs, even though it was causing my heart to stop and giving me terrible side effects. He told me that AF does not cause chest pain and I must be imagining it. He made me feel that I was the problem not the pills. When I asked him about triggers (not even 3 minutes into my appointment) he leaned over and opened the door told me to keep taking the pills and said he did not need to see me again. He knows even less about heart attacks. My immediate neighbour is lucky to be alive - he examined him, never spoke to him and then said to the nurse (in front of him) does this man know the difference between indigestion and a heart attack walked away and signed him out. A few hours later he had a huge heart attack. And Mhairi mt late cousin in law is now dead after his treatment of her AF (granted she caught the super bug when he made an appointment for her to be opened up to see why she was bleeding. She was still on warfarin.....!!! HE never thought....

He is a very arrogant man.. And one that is highly respected in the medical community. But well known for his bedside manner.

Sorry rant over, but I could go on.....

Fran

Richard

From my novice understanding of g proteins to date, they seem to be tied up with the way they affect hydration with salt and water through the intestine. If something goes wrong with them they can get stuck on, or off. I was intrigued to learn that alcoholics often have a problem with their g proteins. Now I don't know if they were born with it, or whether it is a side effect of being dehydrated for too long. But some prior illnesses can cause them to malfunction.

Anyway, it would be great to think that something like AF could be totally put down to better hydration - but I just don't think it is that simple. Otherwise every person in the world who did not hydrate properly would have AF, and that just can't be the case. My husband hardly drinks any water.

The first paragraph in this cut and paste tweaked my imagination... Now to find out which neuroactive hormone it couples.

http://www.swmed.edu/home_pages/news/sprang.htm

New discoveries about G proteins offer insight into molecular basis of human senses, disease
Contact: Morgan Lyons
(214) 648-3404

"The G protein we studied is coupled to the receptors of certain neuroactive hormones produced in human tissue. When activated by the receptor, this G protein acts on proteins that regulate the rate and strength of heart contractions." Researchers so far have identified approximately 20 different G proteins.

In the articles, Sprang and his colleagues, including Chairman of Pharmacology Dr. Alfred G. Gilman, who shared the 1994 Nobel Prize in physiology or medicine for his role in discovering G proteins, showed for the first time the structure of the three molecular subunits that make up the G protein: alpha, beta and gamma. The G protein is inactive when the three subunits are bound together in a complex. Revealing the structure of the complex will eventually help researchers deduce how receptors might pry them apart. The signaling mechanism is expected to be the same for many hormone receptors, as well as for those responsible for basic senses like vision, taste and smell. For example, G proteins help the brain transform the information received by the eyes into images that are seen.

"Individual alpha subunits contain their own internal clocks, which cause them to deactivate after a matter of seconds. In this way they act as a timing mechanism for the receptors," Sprang said.

Earlier research by Gilman, who holds the Raymond Willie and Ellen Willie Distinguished Chair in Molecular Neuropharmacology, in Honor of Harold B. Crasilneck, Ph.D., found that any alteration in the pattern of signal reception or the process of transforming the G protein alpha subunit from its "off" to "on" state, can lead to disease. For example, the cholera toxin alters the G protein, leaving it in the "on" position, which prevents the normal absorption of salt and water by the intestines. The loss of salt and water can lead to dehydration or even death.

To study the structure of the G protein, Sprang and his colleagues grew crystals of the G protein, which were then examined by special X-ray technology, allowing the researchers to map a three-dimensional image of the protein. The scientists described the image of the beta subunit produced through X-ray crystallography as a "seven-bladed propeller." (click to view 115k JPEG version) The design of the propeller graphically illustrates how the beta subunit binds to the alpha subunit and deactivates it.

"We have learned how release of the alpha subunit from the complex turns the molecule 'on,' but we still want to learn how alpha binds to signal receptors," Sprang said. That kind of information could one day make the molecule the basis for new drugs. Sprang believes that drugs eventually will be targeted to G proteins because of the important role these molecules play in controlling essential cell activities.

Fran

From this article and others glutamate is coupled to g proteins (amongst others), which reading between the lines to other articles could affect aldosterone levels - as g proteins and aldosterone have been linked. Let me know if my reading is wrong.

Besides all the research I am following my own observations of my own AF, my own triggers and this seems to explain it.

Cached again

http://216.239.33.104/search?q=cache:xUfZ3jFpTfgJ:www.neurosci.pharm.utoledo.edu/MBC3320/Glutamate.htm+G+proteins+and+NMDA+receptors&hl=en&ie=UTF-8

Ionotropic glutamate receptors
Glutamate receptors are divided into two main subclasses, the ionotropic ligand gated ion channels, and the metabotropic G protein-coupled receptors. The ionotropic excitatory amino acid receptors can be separated further into three groups based on the sequences of receptor subunits and the agonist activity of several ligands. The agonists N-methyl-D-aspartate (NMDA), ibotenate, kainate and quisqualate differentially activate physiological responses at each receptor. The receptors for excitatory amino acids elevate intracellular levels of Ca2+ and Na+ through NMDA, kainate and AMPA receptors. .....

Metabotropic glutamate receptors

The second family of glutamate receptors couples to G-proteins. There are two general classes of metabotropic glutamate receptors. One group (mGluR1 and mGluR5) couple to the stimulation of phosphoinositide metabolism through the Gq family of G proteins. The generation of inositol trisphosphate from posphatidylinositolbisphosphate leads to an increase in intracellular Ca2+ by enhancing Ca2+ release from the endoplasmic reticulum. The other group of metabotropic glutamate receptors mGluR2, mGluR3, mGluR4, mGluR6, mGluR7 and mGluR8 couple to the Gi/o family of G proteins and inhibit adenylyl cyclase.

AP-4 is a selective agonist at mGluR4 and mGluR6 receptors. Agonists at these receptors could be useful as anticonvulsants through blocking the release of endogenous glutamate.....

N-Methyl-D-aspartate and ibotenic acid are potent agonist at NMDA receptors acting directly at the active site. Binding to NMDA receptors is regulated by Mg2+ (increased) and Zn2+ (decreased) as well as by glycine and polyamines such as spermine and spermidine. Glycine is an indirect agonist that enhances NMDA agonist binding through an accessory binding site similar to the benzodiazepine site for GABAA receptors. Kynurenic acid and its 7-chloro-derivative can reverse the positive modulatory effects of glycine at the NMDA receptor.

Now if these G proteins were malfunctioning could it be the basis for LAF ????.....

And in hindsight, re-reading the above article this paragraph jumped out as a possible reason for the cyclical nature of some AF if the g proteins were malfunctioning.

"Individual alpha subunits contain their own internal clocks, which cause them to deactivate after a matter of seconds. In this way they act as a timing mechanism for the receptors," Sprang said.

Fran, Still looking for answers
