WHY THE EPI-PALEO DIET IS STAT PAGING YOUR BRAIN?

READERS SUMMARY:
1. If it was not a quantum biologic effect what was it then?
2. If you have a problem remember what should you consider?
3. How does low cholesterol make your brain soft?
4. Why carbs are not helping you either?
5. What is a Prostaglandin and does a ketogenic diet help that too?
6. How should I eat as I age?

The scene is set in a bad brain or an aging brain is as follows:

My last post dealt with the origins of the ketogenic diet and how it has tremendous beneficial affects on neurodegenerative conditions and many psychiatric conditions with origins in the brain. Today we are going to explore the biochemistry of why this is the case. We talked about a possible quantum effect but today we will deal with some biochemical reasons. We also have seen that the ketogenic diet also allows neurons to uncouple cerebral blood flow from cerebral metabolic rates of oxygen consumption. This affords a huge metabolic advantage for disease neurons. All diseased neurons tend to exhibit huge increased "leakiness" from the first cytochrome in their mitochondria. If you remember from my series on mitochondria, leakiness of this electron transport increases the inefficiency of ATP generation for neurons. This inefficiency in neurons is signaled clinically by an increased CMRO2 in the brain. Cerebral autoregulation mandates that CMRO2 and CBF remain coupled through most mean arterial blood pressures (MAP) from 50 ~160. In neurodegeneration, we see increased inflammation due to the mitochondrial leakiness but with a decrease in CBF. This is why we see hypo-perfusion in parts of the brain with damage on PET scans and fMRI's. This is the direct cause of neurologic and cognitive decline we see clinically. It means the damaged neurons need a higher cerebral blood pressure to maintain perfusion and cognition. This is why the early stages of most neurodegenerative diseases we see elevated blood pressures due to carotid atherosclerosis. As neurons die with time via apoptosis the need for the higher CBF is reduced because metabolic demand is reduced from a shrinking brain.

We will use Alzheimer's disease (AD) as a model from here on out to discuss why the ketogenic diet offers huge protective advantage in most cases we may see clinically. A ketogenic diet is very high in fat content and in cholesterol. Animal cells exploit this property to great advantage in orchestrating ion transport, which is essential for both mobility and nerve signal transport. For many years it was believed that the blood brain barrier blocked lipid transport into the brain. This is why many believed that the brain had to run predominantly on glucose. (Listen up vegans!) We now know this is completely false and, in fact, the brain runs much more efficiently on ketone bodies. Why does it? Special astrocytes (CNS neurons) have an LDL receptor that allows them to absorb cholesterol directly from the blood stream for use in the brain. The brain is made up predominantly from lipids

to begin with. It has also been shown that when blood cholesterol is low, the astrocytes even have the capability to upregulate transcytosis in their membranes to get enough LDL for the brain. Hence, astrocytes are capable of obtaining cholesterol, fats, and antioxidants directly from LDL in the blood-stream. The ApoE4 allele has been associated with the development of AD. This allele has been shown to be associated with reduced cholesterol uptake by astrocytes in the hippocampus (memory center of the brain). ApoE4 /LDL is recognized by astrocytic receptors and transported intact across the endothelium of the blood brain barrier. The ApoE4/LDL molecules that are glycated by high levels of blood glucose, however, will not undergo transcytosis and be left in the blood and have to be deposited in arterial walls and in adipocytes (fat). This is why ApoE4 is heavily associated with atherosclerosis and heart disease progression some believe. I discussed this briefly in Dr. Williams Davis blog on July 31, 2011. Read the comments section and look for my response. This also explains why people with this allele have higher levels of LDL in the blood. The liver responds in kind, with increased production of LDL, to meet the metabolic demands of the brain for lipid. This is a compensatory mechanism that the body is using to offset the depletion of cholesterol in the brain due to glycation (AGE's or ALE's). Clearly, use of a high dietary carbohydrate and PUFA's load stresses this system. This stress is magnified in the mitochondria. The reason for this is found in lipid biochemistry. I know your head is starting to hurt but you will really understand why cholesterol is needed badly in the brain soon.

The most important role of cholesterol in humans is its unique ability to allow freedom of movement to ions in cell membranes because of its chemical composition. It has both a lipid and polar component that allow it to have diversity of chemical benefits in animal cells. This allows the molecule of cholesterol to have both fat and water soluble abilities in our bodies. This allows for the formation of" lipid rafts" in tissue that allow for ion transfers. In fact, insulin is taken up into muscle cells because of the presence of these cholesterol lipid rafts in the membranes! Plants contain no cholesterol at all. Moreover, all of our hormones in the human body are also made form cholesterol. Hormones are the manner in which the brain is able to control the 20 trillion cells in our body. Its importance cannot be more apparent. Our liver is designed to make the LDL our brains need to thrive.

As we all know, neuronal cell membranes are very excitable due to their ion channel chemistry. This allows them transmit signals. A depletion of cholesterol in neurons directly affects the ion channels in their cell membranes. The less cholesterol that is present the more small ions like (sodium) Na and (potassium) K leak out and decrease efficiency of the neurons function to signal. This stressor is directly tied to the mitochondria because of the potential change in the membrane voltage. It directly depletes the neurons ability to generate energy. A decrease in energy or metabolism is directly coupled to cerebral blood flow. Remember the brain is the ultimate energy hog. Cholesterol, therefore is, a fabulous insulator of the excitable membranes like neurons! It confers huge advantages in transmission of nerve signals. Much like an insulator of an electrical wire functions in your house, cholesterol is an insulator that saves the neuron tremendous energy. The covering reduces energy loss. With reduced cholesterol, the neurons

energy expenditure rises quickly. We see this clinically on EEG studies of AD patients where they lose voltage on the EEG and the signal shrinks. Moreover, this is transmitted to the synaptic cleft and we see a resultant drop the neurotransmitter Acetylcholine. Not only that, at nerve synapses cholesterol is used in the neurotransmitter vesicle to release the neurotransmitter into the synaptic cleft to signal other neurons. This reduces nerve to nerve communication further causing declines in cognition.

The energy requirement is born directly by the inner membrane of the mitochondria where electrons must be constantly fed to oxygen to generate ATP (electrons come from food)…….if this breaks down it becomes a major cellular stressor and will use up cellular antioxidants (glutathione, SAMe melatonin, progesterone, oxytocin) to offset the damage. For a time it can hold up (4-5 minutes), by using the antioxidant systems, but it eventually fails, and this failure induces cellular protein folding events that make insoluble protein fragments more prominent in neurons (tangles). Those fragments lead to cell death. As neurons die, CBF is reduced because of the tight coupling to CMRO2 in neurons. I think you can see that a ketogenic diet offers another way to offset the energy inefficiency of cholesterol loss in the brain. It provides a steady supply of fats to insulate nerves and decrease energy drain. This is a key reason why ketones offer the brain a way out of this energy nightmare. Since it uncouples CBF from metabolism it can boost CBF to increase ATP production even as diseased neurons are dying at high rates. That is precisely how a ketogenic diet helps the diseased brain.

Another metabolic advantage of the ketogenic diet is at the astrocyte footplate. Since the body is now using ketones to generate energy over carbohydrates there is much less glycated LDL (diabetes) present in the blood. These unglycated LDL molecules are readily taken up by the "cholesterol starving brain" and used to reassemble the neurons architecture and lipid rafts and ion channels to restore optimal energy balance. It has been shown by Haines in 2001 that in vitro studies a loss of cholesterol in the cell membranes increase its permeability to potassium ion loss by 19 fold compared to normal cells. Eventually this ion loss increases and begins to affect other cell membrane transporters like calcium and magnesium which are larger ions. When this occurs more massive damage occurs in the cell and we see wide spread neuron death due to apoptosis since influx of intracellular calcium is a major signaling event for apoptosis. So as AD progresses its progression increases much faster than it first began. This biologic affect follows its clinical progression and why AD is progressive with time.

To further support the metabolic decline in neurodegenerative disorders, we have this interesting finding. In normal brain aging we see increase dolichol production and a decrease in the antioxidant ubiquinone (reduced form of CoEnzQ10) In AD, the situation is completely reversed, with decreased levels of dolichol and increased levels of ubiquinone. The reason is clear now. Dolichol is produced directly from high levels of cholesterol production in the aging brain for cellular division and maturation during stem cell activation to replace senescent cells. This occurs at the ependymal surface of the ventricles in the human brain with progesterone, oxytocin, melatonin and brain derived growth factor (BDNF) act as co-factors. The stem cells in

the brain are microglia whose footplates are positioned into the cerebrospinal fluid (CSF). The CSF is used as a conduit to allow hormones to signal the microglia to divide to replenish brain cells. Often this occurs during sleep during autophagy. Those chemicals penetrate the blood brain barrier at the circumventricular organs of the brain we learned about in a previous blog. Ubiquinone (reduced form of the antioxidant) is decreased in the aging brain because there is no high stress signaling coming from the mitochondria. Dolichols are the major lipid component (14% by mass) of human substantia nigra (SN) and are important in Parkinson's disease development. A ketogenic diet also increases the amount of BDNF and hormones in the CSF of the brain as well to help replace damaged cells. This finding is why longevity is conferred to those with the higher cholesterol levels found in ALS, heart failure (Framingham study), AD and in PD. It has never made any sense to me why cardiologists do not exam the brain data closely about longevity because it is clear higher LDL levels are protective of life and don't confer a shortened lifespan even from heart disease. It also follows, with this evidence why higher cancer rates are associated with LOWER cholesterol levels. Cancer is a disease of cellular stress hence it is associated with lower cholesterol levels. This result has been found in numerous studies in the literature's well.

Now for some other biochemistry tied to the PUFA's or omega 6 biology and prostaglandins and linking it to the ketogenic diet. Rub your head right here and put Pandora on listen to Fragile by Sting.

Prostaglandins vary somewhat from one another based upon subtle differences in their chemical structures. These small variations are believed to be responsible for the immense diversity of effects they have on the body. Prostaglandins act in a manner similar to that of hormones, by stimulating target cells into action. Where they differ from hormones in that they act locally, near their site of synthesis, and they are metabolized very rapidly to non functional compounds. Interestingly, the same prostaglandins can act differently in different tissue and organs.

Since prostaglandins are only active for a short period of time before they are modified into a non-functional form, tissues cannot store prostaglandins. They are made locally on an as needed basis. Also, many prostaglandins induce inflammation and the constriction of muscle tissue, while certain prostaglandins are believed to be involved in the inhibition or promotion of activities such as ion transport, cell growth, temperature regulation, and immune system response. Prostaglandins are described in series. There are three series.
Series 1 reduce inflammation, dilate blood vessels, and inhibit blood clotting. The strong anti-inflammatory properties help the body recover from injury by reducing pain, swelling and redness.
The Series 2 prostaglandins play a role in swelling and inflammation at sites of damage or injury. They also play a role in inducing birth, in regulating temperature, lowering blood pressure, and in the regulation of platelet forming and clotting. The role of Series 2 Prostaglandins does serve a vital role for the body for without it you would bleed to death from the slightest cut. However, in excess (think high omega 6 content of the diet), these

prostaglandins are harmful and many diseases are directly linked to excessive inflammation and blood clotting.
The Series 3 group has a modulating effect of the stress response in the local organ. This brings the local reaction to an end.

More recent research has focused on the balance between Series 2 and Series 3 prostaglandins. The Series 2 group is involved in intense urgent actions , often in response to some emergency such as injury or stress. Now to tie the ketogenic diet to these chemicals…

The organic chemistry of the success of the ketogenic diet is based upon the following. Dietary fasting or the use of high dietary MCT's (coconut oil), stimulates the beta oxidation (fat breakdown in mitochondria) of very long chain fatty acids that occurs in most neurodegenerative disorders and some disorders with developmental delay like autism. This action immediately depletes the brain of its lipid supply and causes the prostagladins to be unregulated. Moreover, the use of simultaneous dietary carbohydrate ingestion increases the release of insulin peripherally which depresses delta 6 de-saturase enzyme and stimulates the production inflammatory prostaglandin series two chemicals which destroy the brains stores of DHA and EPA and this slowly erodes the brain's lipid content. This can be offset by increasing transcytosis at the astrocytes **if** there is enough dietary LDL made by the liver. Restricting dietary fat by choice or using statins exacerbates this problem and will cause further cognitive decline. We should encourage the liberal use of cholesterol laden foods and foods high in MCT in these cases. Any excess of dietary PUFA (polyunsaturated fats) made from omega 6 fats worsen the situation further. These are the series two prostaglandins from excess dietary omega 6 fats. This is why I advocate checking a patients omega 6/omega 3 level ratio on the blood test often. I check mine quarterly. Ideally we want this number 2/1 to 6/1 for optimal human health. I personally shoot for a 1/1 ratio. Moreover, as we saw with cholesterol transport and the LDL receptor, blood glucose from dietary carbs also compromises the production of the good prostaglandins for lipid synthesis in the brain. So when you order your O6/O3 ratio you should also want your fasting insulin level as close to zero as possible. Below 3 is acceptable for most but if you have a neurologic disease you really need very tight control of your insulin to restock the brain with lipids.

The Series 3 prostaglandins are formed at a slower rate and work to deal with excessive Series 2 prostaglandin production. They act to turn off the inflammatory cascade that the series two PG's cause. Series 2 prostaglandins are often called antagonistic prostaglandins because they counter balance PG series one. All antagonistic prostaglandins are made from a fatty acid called arachidonic acid (AA). Series 1, or beneficial prostaglandins are made from a fatty acid found mostly in marine plants and fish known (grass fed beef) as EPA. EPA is the most important member of an exclusive group of three fatty acids called the "omega-3 fatty acids" that include ALA, EPA and DHA. These fats are critical building blocks in lipids for the brain.

ALA is made in the chloroplasts of green plants from linoleic acid. In mammals, linoleic acid is converted to arachidonic acid that is used to make the antagonistic prostaglandins. BUT, in the green plants, the same linoleic

acid is converted into the beneficial ALA. (Think flax) Mammals are not good converters of ALA from plants so that is why it is not optimal choice for your diet or your brain. Wild shellfish, fish, and grass fed beef are our best sources in our diet. Can you say Epi-paleo Rx anyone?

DHA and EPA are the most critical of the omega 3 fatty acids for the brain. It is the only material that our bodies use to make the beneficial prostaglandins that help reduce inflammation. DHA is another omega 3 fatty acid. It is an integral part of eye and brain tissue in collecting electrons. It is made by marine algae, plankton, fish and mammals from EPA. Fish accumulates DHA in their oily tissue, along with EPA. As I laid out in my posts about the causes of AD and PD the causes of these diseases destroy the brains lipid stores while simultaneously increasing inflammation, depleting cholesterol in the face of an elevated omega six from our diets. I believe once you understand this cascade, if you eat in such a way to avoid this cascade you can treat these diseases. If you have a family history of these diseases you can completely avoid it but eating a VLC ketogenic diet.

WRAP UP:

Here I have laid out two biochemical reasons why a ketogenic diet works in our brains to increase cognition. It also makes sense why in neurodegeneration we see brains starved of cholesterol and DHA levels. The ketogenic diet is the best and most ideal way to restore both of these key fats to the brain in this time of stress to increase cognition.

The bottom line is as you age, the evidence is accumulating, that you should be eating a more ketogenic diet with a liberal amount of saturated fat in MCT (coconut oil and pastured butter) and one that supports a substantial production of LDL from your liver via your diet…that is also devoid of glycosylation from carbohydrates. This describes the Epi-paleo Rx well. It is a version of the ketogenic diet. If one has a formal neurologic condition a more stringent version of the paleo diet should be entertained. But if you are interesting in optimizing for longevity as you age a ketogenic diet confers huge advantages. If one is a performance athlete, a ketogenic diet may not be the best diet for you long term. If you are overweight and wish to shred weight this option is an excellent choice. As always, discuss this with your doctor before deciding what to do. I recommend the book "The Epi-Paleo Rx" to my patients as a resource to get them started on what foods can lead to a disease reversal best.

So how should we consider eating as we age when neolithic diseases increase in incidence and prevalence?

1. First, eat marine fats (MCT and saturated fats, PUFA's last to decrease inflammation) then consider moderate protein (controls mTOR pathway) and then low carbs (to decrease inflammation and glycation)
2……and those macro's should increase as one ages for health and longevity to keep your hormones in the best balance they can be. Remember every single hormone we have are made from cholesterol!!!! If you go into aging with hormonal imbalance due to a bad diet, you will age much faster. If you eat a SAD you will age and die much faster of neolithic diseases.

3. Everyone should consider checking their omega6/3 ratio at some point with a HS CRP level to determine the amount of inflammation in their body to make good dietary adjustments.
4. I completely reject the lipid hypothesis and diet heart hypothesis as they currently stands. I think this blog makes you understand why. You may want to consider throwing your statin Rx away at some point. The data on statins for people over the age of 60 without any risk factors says no one should be on a statin based upon the data. Only those people who listen to the opinions of cholesterol panelists that have ties to big pharma will tell you its a good thing to do. The older you get, the more DHA and LDL your brain needs, and the less carbohydrate it needs.

CITES:

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2. http://bms.ucsf.edu/sites/ucsf-bms.ixm.ca/files/varoninjillian_04072011.pdf
3. http://onlinelibrary.wiley.com/doi/10.1111/j.1471-4159.2010.06768.x/pdf (cholesterol deficiency decrease synapse vesicle recycling)
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