

# Your Gut, Neurotransmitters, and Hormones

## READERS SUMMARY:

1. HOW YOUR GUT BRAIN AND RESPONSE OF YOUR BRAIN ARE ALL TIED TOGETHER?
2. WHAT ARE THE 4 MAIN NEUROTRANSMITTERS?
3. WHAT DO THEY DO AND MEAN?
4. WHAT AFFECTS THEIR PRODUCTION?
5. HORMONES ARE THE BRAINS ENDOCRINE SECRETION THAT TELLS YOU HOW YOUR EPIGENETIC SWITCHES ARE SET.
6. HOW WE USE HORMONE STAUTS TO FIGURE OUT WHAT IS REALLY WRONG WITH YOU?

The next post in the series follows directly upon what we learned about the brain and ketogenic diets. Today we are going to mesh the brain gut axis and neurotransmitters so you can begin to understand how diet can modify your personality and your behavior. In severe cases it can also cause mental illness and eating disorders. In fact, if you have never heard of the GAPS diet you need to read a bit about it. Today I will lay out some of the biologic plausibility of how this occurs and some interesting clinical correlates to specific NT deficits from our diets. Everything in biology usually ties back to the brain at some point and this is very clear in NT biology. Neurotransmitters are involved in many neural circuits in the central and peripheral nervous system. They are also found in the autonomic nervous system and in the enteric neural circuits in our guts.

There are four main neurotransmitters (NT) in the brain and we will focus on them to make some general principles clear. They are Serotonin, Acetylcholine, GABA, and Dopamine. There are quite a few other neurotransmitters but I don't want to overwhelm you the biochemistry of this class of molecules

because it is quite complex and, at this point of the QUILT roll-out, not all that important.

All the neurotransmitters are made from amino acids from proteins except acetylcholine (Ach). Ach is made from dietary choline or recycled choline and acetyl groups from the Krebs cycle. All macronutrients are required to make all the parts of NT for proper function. No food group can be excluded and still expect to have proper NT function. Dietary neurotoxins like phytic acid, lectins, excess caffeine, nicotine, mineral depletion, vitamin depletion, and alcohol can affect NT production. Some are made entirely by the body. Some are converted by the biologic machinery we have. If we don't have sufficient supply of certain substrate amino acids (AA) we may actually lack the substrate to construct NT for optimal function. This can lead to changes in mood or behavior when we alter fuel sources or change our diets.

**Serotonin** begins with the AA tryptophan. It requires B6, Mg, B12 and folate as co factors in production. B Vitamins are the major methyl donors in the production many NT so they are vital for brain function and development. If you fail to eat them or absorb them you can bet your ass that you will suffer from serious mental or neurologic issues at some point down the road. **Tryptophan** is the least common AA in our diets. It also happens to be the most difficult to absorb into the brain. This also complicates serotonin biochemistry. Tryptophan is found in fish, poultry, and dairy products but eating these products does not necessarily increase serotonin levels. The reason for this paradox is because other foods compete with tryptophan for absorption in the gut. It has to compete with other AA. In fact, another paradox of serotonin production is that is eating carbohydrates raises its level in the body faster than does eating a protein diet! The reason for this is that carbs stimulate insulin release and this insulin spike favors the absorption of tryptophan in the gut over other amino acids. So this is a reason why eating some

carbs is important. Many zero-carbers make a huge error in not realizing this. This helps you understand why people who need serotonin tend to be stress eaters and eat more sweets and starches. Moreover, studies from MIT, Harvard and Oxford have shown that women on a high protein and low carb diet are more prone to low serotonin levels. In the paleo world this is called the "low carb flu." This is easily overcome when you change your diet by using 5-HTP for about two weeks to adjust to your new diet. If the person was previously seriously serotonin depleted this could cause initial weight gain while dieting, severe cravings, bingeing, bulimia, and severe PMS. I have even seen a flare up of seasonal affective disorder myself.

Men are 52% more effective in absorbing tryptophan than women too. Most serotonin is stored in the enterochromaffin cells of the gut lining (60%) and the balance is stored in the pineal gland of the brain. The gut is used as a storage site when to restore the brain when it is needed. Dietary carbs may play a big role in brain health. Dr. Judith Wurtman from MIT has published many articles linking low carb diets to deficiencies in serotonin and causing mood disturbances but there is some controversy about her theories. In fact, there appears to be a pronounced difference in gender. Women tend to make 30% less serotonin than men. Many believe this due to their lower growth hormone levels and higher leptin levels. Women maybe more susceptible to mood changes on low carb and high protein diets. This point is not set in stone.

Dopamine is made from the AA tyrosine. Eating a high protein diet promotes dopamine production. It is abundant in poultry, meat, dairy products, almonds and avocados. It's why we formed our large brains from an evolutionary point of view. Dopamine is the NT of our newest part of our brain, the frontal lobe.

The majority of tyrosine that does not get incorporated into proteins is catabolized for energy production. One other significant fate of tyrosine is conversion to the catecholamines (NE, and EP). The catecholamine neurotransmitters are dopamine, norepinephrine, and epinephrine used in stress response tracts. The NT production line uses methyl transfers at several steps to accomplish this and it should be clear now why B vitamins are critical to neurons. They are the substrates that donate these methyl groups to make the final neurotransmitters.

Dopamine levels in the brain directly correlate with voltage intensity on an EEG exam. An EEG is a test we neurosurgeons or neurologists use quite often to assess patients. For example, a mother who was an alcoholic during pregnancy causes epigenetic signaling in an unborn fetus and predicts an obesity pattern for the unborn child due to a dopamine deficit. Children who are born dopamine deficient tend to crave sweets to increase their brains voltage via their reward tracts but the food can never replenish the lost power. This is especially powerful when the hypothalamus never becomes sensitized to leptin by breastfeeding. Remember your mom's colostrum contain her leptin that acts as a USB drive for your brain to be set. If your mom is leptin resistant or your mom does not breast feed you, your brain begins at a disadvantage at birth. It can still be overcome but most of the time it is not because of the use of baby foods with crap in it (similac and Gerber's). Epigenomic programming for leptin resistance has been shown to heavily influence the future dopamine status in the brain reward centers of the brain. Leptin and dopamine are coupled in the brain at the hypothalamic level. When leptin is released from adipocytes and it is properly signaled in the hypothalamus it immediately decreases reward behaviors for food seeking and the person will stop eating much sooner. This is commonly seen in diets with high protein and fat contents especially at breakfast within thirty minutes of waking. People low in dopamine tend to crave caffeine to a

great degree. Addictions of all types are associated with dopamine deficits and damage at the hypocretin neurons in the hypothalamus. The expected phenotype of someone with low dopamine levels is usually an adult with high cortisol levels and copious amounts of abdominal obesity and many neolithic diseases. Another interesting clinical correlate I have found is that in patients with dopamine deficiency are very deficient in the hormone substrate pregnenolone. This occurs at a very early age as well and is the major predictor of future hormonal imbalance in my practice. Adding it back to their diet tends to accelerate their weight loss. I believe this is because of the high levels of cortisol from the long term leptin resistance that underlies their obesity type in the hypothalamus.

Acetylcholine was the first neurotransmitter discovered and is the major neurotransmitter in the peripheral nervous system. Acetylcholine (Ach) is the NT that tends to control processing speed in the human brain. Brains high in Ach usually are razor sharp. This is the NT that is lost most severely in Alzheimer's disease. It allows for quick reaction time and thinking. Ach production is tied to dietary fat intake especially cholesterol and saturated fats. The Acetyl CoA comes from metabolic breakdown products of glucose and fructose and the choline comes from phosphatidyl choline, the major phospholipid in the membranes of plants & animals (but not bacteria). The choline is absorbed directly across the blood brain barrier as I laid in my my recent post by astrocyte foot plates. Eggs and organ meats are rich in substrates for Ach production. Choline is found in high concentrations of both egg yolk and offal. It is in the B vitamin family. B5 is a co factor in its synthesis as well. Vitamin B5 enhances the ability of Arginine to stimulate the release of human Growth Hormone as well during slow wave sleep (hGH).

What can one expect clinically if you are deficient in Ach? Your ability to think will be slower. Memory lapses more

common and you may notice more frequent trips to the restroom for bowel movements and urination. Sexual dysfunction also is more common. The phenotype of those with Ach deficits are that of a "worry wart". Ironically, they never seem to care a lot for their own well being though. They tend to be nurturing and perfectionists with little initiative and quite inflexible. Ach deficiency is a real problem in menopause and andropause because the sex steroids are Ach stimulants. So as the sex steroids drop as we age, mental processing speeds slow. Ask any menopausal woman if this is not a common symptom. I know because my practice is filled with them. This is clearly seen as the "cognitive haze" as hormones fall in perimenopause and andropause. This has been occurring earlier in life in the USA due to the rise of diabetes and those with high cortisol levels. High cortisol levels lead to rapidly falling sex steroids and vitamin D levels due to pregnenolone steal syndrome. The falling vitamin D levels also appears to play a role in the development of autism spectrum disorders and autoimmune conditions. As cortisol rises, this worsens the ACh deficit and cognitive decline becomes more evident. Persistent cortisol elevation further destroys the gut surface and makes it more permeable to inflammation and this worsens the NT deficits over time. This becomes a serious positive feedback loop. Moreover, in the USA with a SAD we are seeing earlier onset perimenopause because of the combination of low fat diets and simultaneously declining sex steroid hormones from pregnenolone steal syndrome. The response of many physicians is to treat patients with anti-depressants medications but what they need is a return to a higher fat diet. I ask my older patients to eat 60-75% fat diets until they normalize. They all looked at me shocked based upon the CW they have heard until I explain WHY? There is a current epidemic of low vitamin D in the USA that is being recognized but not accurately treated with dietary modification. Adding dietary fats back can really change these biochemical processes and patients behavior

quickly. Hormone levels are the best way to assess epigenomic switch settings. It tells us precisely how the brain is partitioning calories based upon its current deficits.

GABA is  $\gamma$ -Aminobutyric acid. GABA deficiency has been linked to anxiety disorders, panic attacks, addiction, Parkinson's syndrome, cognitive impairment, insomnia, headaches, and seizure disorders like epilepsy. GABA is our natural "off" button to life. It is the NT of relaxation. GABA directly counter balances the stresses of life from dopamine and serotonin. GABA is made from glutamate, but not in the gut. GABA does not penetrate the blood-brain barrier; it is synthesized in the brain and spinal cord. It is synthesized from glutamate using the enzyme, L-glutamic acid decarboxylase and pyridoxal phosphate (which is the active form of vitamin B6) as a cofactor via a metabolic pathway called the GABA shunt. The way to increase GABA in the brain is by supplementing its precursors properly, namely Pyridoxal Phosphate, the active form of vitamin B6. B6 usually comes in animal proteins of the diet (sorry Vegans!). One of the key modulators of GABA is Taurine. Taurine, itself a powerful inhibitory neurotransmitter helps balance and control the effectiveness of GABA in the brain.

This brain process converts glutamate, the principal excitatory neurotransmitter, into the principal inhibitory neurotransmitter of the CNS, GABA. This inhibitory NT is involved in controlling brain rhythms and muscle tone. People deficient in GABA tend to eat quickly and often. They often struggle with portion control of their meals. They often taste their food when cooking and rarely miss any desserts. GABA has many varied biological affects in the brain. This occurs because of its unique organic chemistry. The chemical conformational flexibility of GABA is important for its biological function, as it has been found to bind to different receptors with different conformations. Many GABA analogues with pharmaceutical applications have more rigid structures in order to control the binding better but this affects their

neurochemistry in vivo. In fact, this neurotransmitters' biologic diversity of action is tied to its quantum chemical behavior. Yes, more evidence that quantum biology plays a role in the human brain. GABA is found mostly as a zwitterion, that is, with the carboxy group deprotonated and the amino group protonated. Its conformation depends on its environment in the brain and spinal cord. The stabilization is about 50 kcal/mol, according to quantum chemistry calculations.

## **Wrapping it all up.....**

*What affects neurotransmitter formation in humans?*

1. **Stress/Cortisol.....**this depletes transmitters and increases their turnover especially over training and obesity

2.

**Aging.....**60% of all adults past 40 years old have some degree of neurotransmitter deficiency. Aging neurons also make less NT than young ones.

3. **Improper dieting.....**limiting food groups dramatically affects brain chemistry within three weeks.

4. **The leaky gut.....**probably the largest single cause of NT loss and deficiency due to altered absorption and inflammation at the brain level. This is the source of the GAPS diet. Glutamate, glycine, arginine and ornathine are incredibly important AA for gut integrity. A paleo diet provides us with these in abundance.

5. **Abnormal sleep.....**generates IL-6 and alters the conversion of serotonin to melatonin and leads to serious depletion of DHEA in most people with sleep disturbances.

6. **Medications....**diet pills, stimulants, recreational drugs deplete NT's, ephedra and ma huang deplete NT's

7. **Neurotoxins.....**heavy metals, pesticides, BPA, cleaning solvents, ecstasy, nicotine, alcohol, MSG.

8. **Hormones.....**if there is any hormone imbalance there will be major NT production issues in our brains. It is mandatory that bioidentical hormone replacement be considered in tough cases



with stalls and serious mood disorders. Growth Hormone deficiency, which occurs in women at 35 and men around 50, leads to a "leaky gut" by depleting the body of glutamate, glycine , arginine and ornathine from dietary sources. Estrogen can cause a dramatic shift in the production of serotonin or its transport to the brain. DHEA and pregnenolone deficits decrease melatonin production and are very common in those with poor sleep. Progesterone is very commonly seen in poor sleep in women with menopause and men with andropause and exacerbates the ability to learn and neural plasticity as we age. Progesterone directly affects brain derived nerve growth factor needed to make new neurons. In many neurosurgical patients we find dramatic changes in progesterone levels that directly effect recovery from stroke, trauma or tumor repair.

9. **Epigenomics/genomics**....those with epigenetic histories that favor mental illness are notoriously poor in production in some NT production. Drug addiction, autoimmune conditions and alcoholism also can predict future NT disorders. This is likely the major way mental illness affects subsequent generations in my opinion.

10. **The Brain is the key to it all.** Remember we are all losing neurons every single second of the day. In a two hour period, most of us will lose about 6500 neurons! But some of us (AD OR PD) may lose a great deal more. Some will lose 60,000 neurons. Others may lose 600,000 neurons. It's different for every one of us based upon the status of our epigenomic switches in the current settings. There are many factors that contribute to this increased level of destruction as we have seen above.

One of the ways we can counteract the normal loss of neurons is through neuro-plasticity. If we provide the brain with the proper substrates for optimal health and maintenance we can allow our genes to retool the brain while we sleep with the process of autophagy. This is the process by which a healthy brain can change to better cope with the environment it finds itself in now. This is precisely what epigenetics is. If an area of the brain is damaged and dysfunctional, another area

can take over some of the function if we give it the tools to do so. As we fire a specific pathway repeatedly over time, it becomes more and more efficient. This is how we learn. During sleep these pathways become hardwired. If you don't sleep you will learning suffers tremendously. If you don't sleep your metabolism suffers tremendously. If you don't sleep well your much more likely to have mental illness too. It is all based upon the building blocks of how the brain is made. Lipids and NT's are critical to optimal functioning. So, while we are constantly losing neurons, our pathways can become more efficient and responsive to our current environment. We can actually have a higher level of function as we get older. I can tell you as a neurosurgeon people who have adapted their diet to this evolutionary approach I have laid out here have seen their cognitive scores rise. There are specific hormone tests we can use to see the affect of how improving your diet directly affects the brains function and sleep. People who sleep poorly tend to have very low levels of DHEA-S in their blood or saliva. This level correlates well with high levels of IL-6 in the CSF of the brain and blood. Once we correct the diet this all reverses. The easy way to assess it is to ask the patient if their sleep has improved but I want to see how much better with their DHEA levels. That way I can push them harder or slow them down. It just depends on your outlook. I want a straight A for my patients. I don't like settling for a C or a D in anything I do.

#### CITES:

1.

<http://www.rockwellnutrition.com/assets/images/docs/SupportNeurotransmitterProduction.pdf>

2. Kandel & Schwatzr textbook.