



Sleep, Vitamin D, and the Microbiome - Implications for Brain Health

Abstract:

Humans are self-repairing organisms that have evolved within two, planet-derived, repeating loops; the 24 hour daily cycle, and the 365 day annual cycle. Our brain is entrained to the 24 hour, circadian cycle through sunlight entering the eye, using retinoids like vitamin A. We are also linked to the annual cycle by sunlight, but in this case, by sunlight entering the skin, making a hormone called vitamin D. Vitamin D allows us to sleep longer and gain weight in winter by seasonally changing our intestinal microbial populations to promote fat storage and longer sleep (hibernation). The healthy microbiome is made up of a symbiotic foursome of bacterial species that require our vitamin D. They, in turn, produce eight B vitamins that we absorb and use. Normal sleep requires both specific vitamin D blood levels and normal B vitamin-producing intestinal bacteria. Poor sleep is known to predispose to both chronic illness and degenerative brain disease. As normal sleep is the most potent epigenetic modifier of our health and well-being, reversing the pandemic of abnormal sleep should be one of the most important medical imperatives of the 21st century.

Sleep:

In order to understand how the intestinal microbiome is related to normal sleep it is helpful to understand some basic ideas about sleep. The study of sleep in laboratory animals started in the 1950's with a demonstration, in cats, that nuclei in the periaqueductal grey of the brain stem, called the nuclei reticularis pontis oralis caudalis (NRPOC), are responsible for paralysis during sleep. (1) The NRPOC are three groups of nuclei organized by the muscles they innervate; diaphragm and chest wall, bulbar muscles, all other skeletal muscles. This organization allows paralysis of different muscle groups during different phases of sleep.

There are two sleep phases called "deep sleep"; Slow Wave Sleep (SWS) and Rapid Eye Movement (REM) sleep. They are characterized by specific EEG brain wave patterns but they are also distinguished from "light sleep" by paralysis. During SWS the skeletal muscles are paralyzed, but the mouth and throat are not. During REM sleep the bulbar muscles, skeletal muscles and the chest wall are paralyzed, possibly to keep us from crying out during dreams. (1)

Although the actual *purpose* of paralysis is unknown there are several observations that suggest a possible explanation. The release of growth hormone (GH) occurs during SWS. In childhood its sustained release results in growth, suggesting that the moving parts of the body must be paralyzed in order to grow. After growth is completed, GH is still only secreted during SWS, but the pattern of release changes from continuous to pulsatile. (2) By analogy then, if repair is considered similar to growth, it suggests that the moving parts of the body must be fully paralyzed for nightly repair to occur.

There are some obvious difficulties with being paralyzed in sleep. We must be able to swallow our saliva, protect our airway, and breathe normally. We must be able to awaken immediately into a non-paralyzed state to escape a predator. Paralysis seems a pretty risky undertaking. What if a malfunction were to cause the paralysis to occur inappropriately while we were awake? This

malfunction does indeed happen, and is called cataplexy, which means, "struck down by paralysis". Cataplexy is at the very least inconvenient and under certain circumstances potentially fatal.

Clearly the brainstem nuclei that turn off the muscles of the body must be able to turn them on again. That means a malfunctioning NRPOC can also cause inappropriate muscle movement. Inappropriate activation while awake would result in a conscious patient who falls to the ground moving, unable to control their limbs or speak. The term "kineoplexy" or "struck down by movement" seems an appropriate term, though these patients have historically been told that they have "pseudo-seizures". They do look like they are having a seizure but there are no corresponding EEG abnormalities on video EEG monitoring because the malfunction is occurring in the brainstem, not in the cortex. Cataplexy and kineoplexy are two examples of sleep disorders that occur during the waking state due to of malfunction of the NRPOC.

The other sleep disorders that are related to a malfunctioning NRPOC or "paralysis gone wrong" are obstructive sleep apnea (OSA) and periodic limb movements of sleep (PLMS). Over the last 30 years we have focused inappropriately on just the airway anatomy of OSA. But since the bulbar muscles are specifically paralyzed during sleep we should be attending to the NRPOC as well as the airway. In fact, both "too paralyzed" (OSA) and "not paralyzed enough" (PLMS) were first hypothesized to be originating from a malfunctioning NRPOC as early as 2000. (1) Since both of these extremes are often recorded during the same sleep study one could picture the firing rate of the NRPOC as "wobbling" back and forth between; too fast = too paralyzed and too slow = not paralyzed enough. This provides a single, anatomic location for both malfunctions. If the cause of this malfunction could be determined it might also suggest a cure.

The Sleep Switches

Sleep and wake are designed to be two mutually exclusive states. Normal, healthy animals can be in one or the other, but never both. In the electronics industry the term "flip flop switch" refers to a purposeful design that prevents State A and State B from ever co-existing at the same time. This term has been borrowed and applied to these biological "sleep switches". (3)

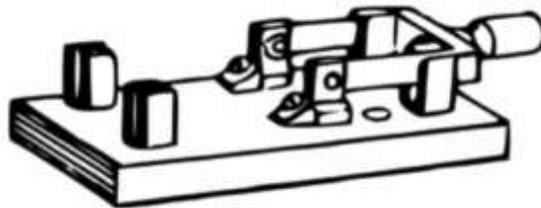


Figure 1. Flip Flop Switch

In reality, the sleep switches are very complex, interconnected brain stem and lower brain nuclei linked by multiple feed-back loops promoting one state while simultaneously inhibiting the other. (Figure 2). These switches govern the timing of and transitions between the phases of sleep. In order to operate normally the "timers" of sleep must be very, very tightly locked to the NRPOC so that paralysis will *only* happen during sleep.

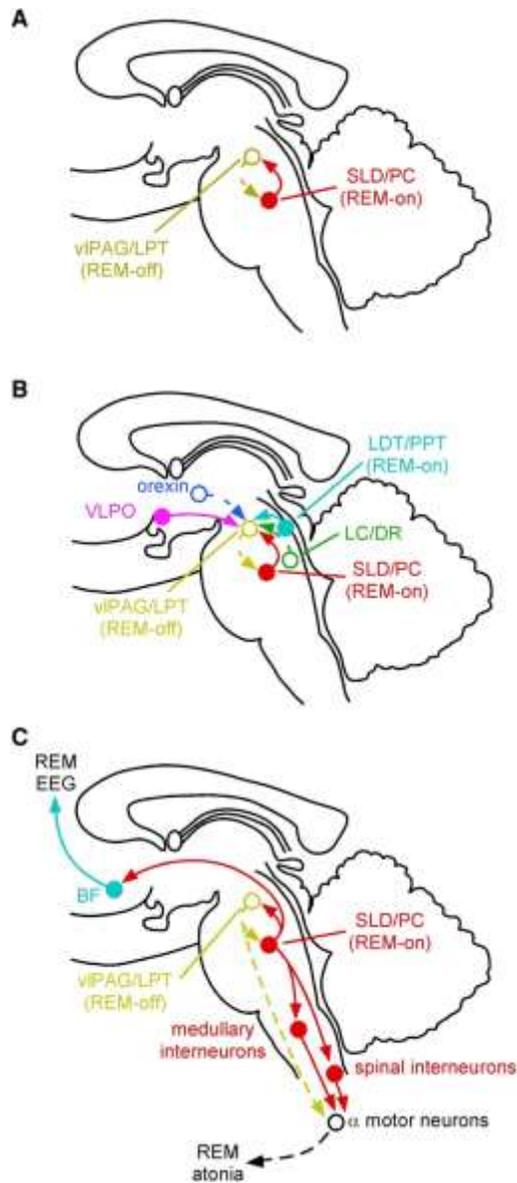


Figure 2: Two populations of mutually inhibitory neurons in the upper pons form a switch for controlling transitions between REM and NREM sleep (A). The core REM switch is in turn modulated by other neurotransmitter systems (B). During REM sleep (C) From: Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep State Switching. Neuron 2010;68 (6)1023-1042

Vitamin D and the Sleep Switches:

Histologic descriptions of vitamin D receptors in the sleep switches (nucleus reticularis pontis oralis caudalis, locus ceruleus, substantia nigra) were published in the 1980’s but then largely overlooked until a clinical link between vitamin D deficiency and sleep disorders was published in 2012. (4-6) Improved sleep was reported by over 1000 vitamin D deficient, daily headache sufferers by achieving and sustaining a vitamin D blood level of 60-80ng/ml. These patients all had abnormal sleep studies characterized by absent or reduced REM or REM-related apnea. (6) Explanation for this positive vitamin D- sleep effect may relate to the production of acetylcholine

(ACh) as activation of the Vitamin D receptor in the NRPOC produces the enzyme Choline Acetyltransferase, responsible for the final step in the production of ACh. (7).

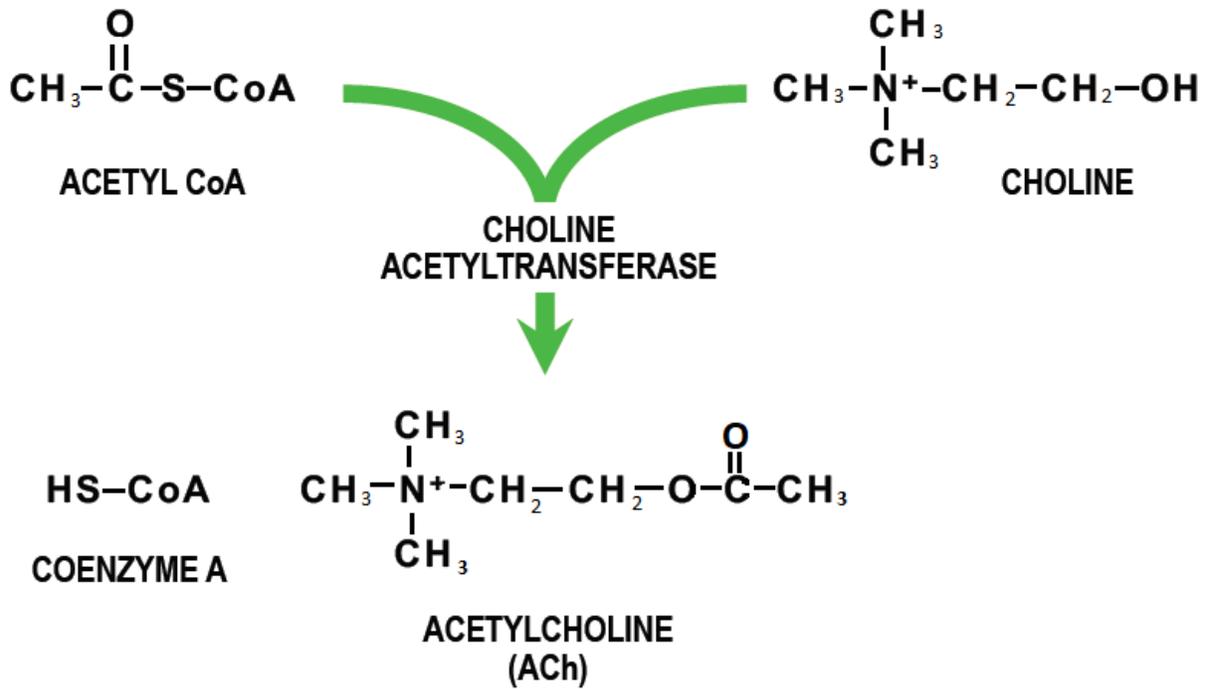


Figure 3: The Synthesis of Acetylcholine.

The Intestinal Microbiome and Sleep:

The number of roles assigned to the intestinal microbiome seems to grow larger by the day. Apparently we are more accurately viewed not as the sophisticated individual we thought we were, but instead as a group! A living, breathing, mobile, multiple-specie being made up of a single mammal incorporated into or living-in-harmony-with multiple populations of viruses, bacteria, and fungi who share our lives and help and protect us in multiple ways. (8-19) Perhaps even living inside our brain sustaining our brain health. (20,21) The intestinal microbiome also plays a pivotal role in our sleep, probably through its production of B vitamins.

B Vitamins Supplied by the Intestinal Microbiome:

There are articles documenting that each of the B vitamins has both a food source and an intestinal bacterial source. (22) But, the first group to propose that the four normal intestinal bacterial species; Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria show up together consistently *because* they make and share the 8 B vitamins, proved their idea in a very innovative way. (23) Though only 2 % of the over 200 intestinal species that occupy our gut have ever been grown in a petri dish we do have extensive DNA libraries of each.(24) In other words we know little about their normal growth requirements but we know a lot about their DNA.

Using bacterial DNA libraries Magnusdottir, et al were able to show that each of the four groups of normal intestinal bacterial species had the genes necessary to make the enzymes needed to



produce at least one B vitamin, and also lacked the enzymatic machinery for another required B vitamin. (23) Their summary: “This analysis suggests that human gut bacteria actively exchange B-vitamins among each other..... We propose that in addition to diet, the gut microbiota is an important source of B-vitamins, and that changes in the gut microbiota composition can severely affect our dietary B-vitamin requirements.” (23)

Historically the B vitamins were first described as *bacterial growth factors*. The very early microbiologists used the rather quotidian cultures of yeast and bacteria used to make beer and bread as their growth medium to grow and learn about bacteria. (25) Over time, the multiple growth-promoting chemicals supplied by that fermentation mixture were identified and numbered as a “group” of growth factors called the B vitamins. That same fermentation mixture was, at the time, called the “anti-polyneuritic factor”, and was used to treat burning in the feet. Eventually the eight chemicals that were originally used to promote bacterial growth were found to be necessary for human health as well. (25) Apparently we never needed to be able to make these 8 chemicals because we always had the source inside us.

Connecting B Vitamins, the Microbiome and Sleep:

The patients who took part in the vitamin D-sleep trial referenced above were followed for an additional four years. (26) Despite maintaining a blood level of 60-80ng/ml the beneficial D-sleep effect began to wane after two years, sleep problems returned and new symptoms of muscle and joint pain as well as neuropathic burning in the hands and feet began to appear.

1950’s experiments blocking the absorption of pantothenic acid (B5) produced a clinical triad of insomnia, puppet-like gait and burning in the feet. (27-29) The discovery of these observations led to a small, uncontrolled trial of 400 mg of B5 in combination with B100 (8 B’s, 100 mg or mcg) in approximately 40 patients who had been using D for two years.(26) The results were immediate, but unexpected. The two patients with unexplained burning in the hands and feet were rapidly symptom free, but the majority of the participants complained that the 400 mg dose of B5 immediately made them agitated and *unable to sleep*. Most stopped it after 1-2 days. Upon continuing B100 alone however, there was rapid improvement in sleep and pain suggesting a very narrow dose range for B5. The unexpected symptoms of agitation and insomnia produced by the “recommended” dose of 400 mg of B5 suggested that the D supplementation may have affected the response to B5. (unpublished, personal observation, see below)

This successful, smaller trial led to a larger, uncontrolled trial in over 5000 patients with a variety of sleep disorders. Vitamin D supplementation at a dose to maintain the D blood level at 60-80 ng/ml, in combination with B50 (½ B100) or B100 led to significant improvement in sleep complaints, regardless of the type of sleep problem. (26) Though patients with irritable bowel complaints had no improvement while supplementing with D alone the addition of B50 or B100 led to rapid improvement in abdominal complaints in most patients. Importantly the large dose B complex had to be withdrawn at the end of three months to avoid re-emergence of the same symptoms of morning pain and sleep disruption. This suggested that a combination of vitamin D and all 8 B’s had successfully created an intestinal environment that favored the return of the normal microbiome. The healthy foursome, once again the dominant species, were producing the

normal amount of B's and continuing oral supplementation past three months resulted in double dose B5 and a return of sleep issues.

Pantothenic Acid:

“Pantothenic acid deficiency does not exist because it’s ubiquitous in food”, is the currently accepted dogma. This was probably a safe assumption when most of the human population had a normal intestinal microbiome, but it is coenzyme A (CoA) that is actually ubiquitous in food, and CoA is not absorbed in that form. It is the D enantiomer of B5 that is absorbed from the gut. (30-33)

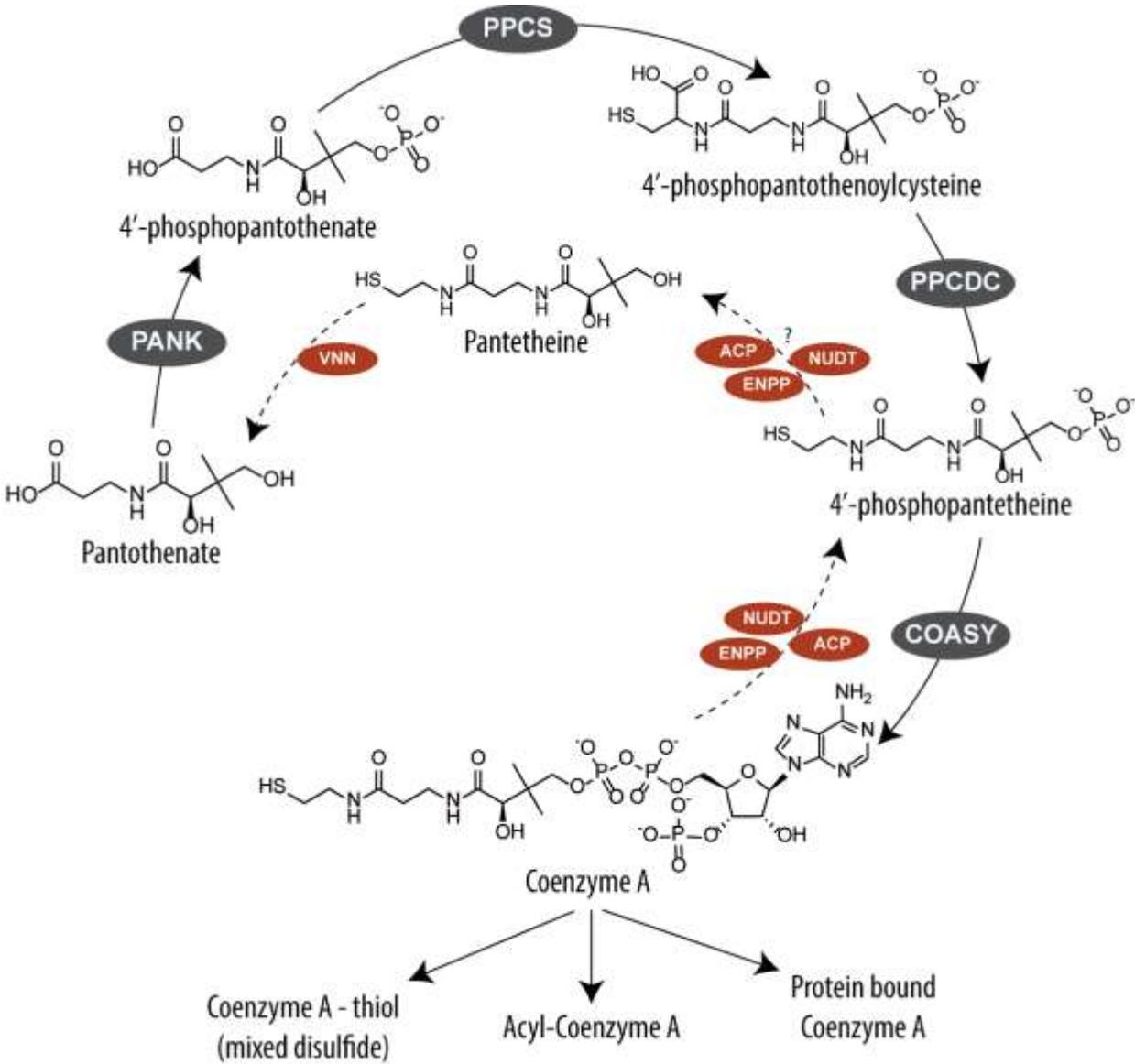


Figure 4: Overview of CoA de novo biosynthesis, degradation and utilization homeostasis. Canonical de novo biosynthesis pathway representing the substrate pantothenate which is phosphorylated to 4'-phosphopantothenate by pantothenate kinase (PANK). Subsequently, cysteine



is added by 4'-phosphopantothienoylcysteine synthetase (PPCS) to form 4'-phosphopantothienoylcysteine, which is then decarboxylated by (R)-4'-phospho-N-pantothienoylcysteine decarboxylase (PPCDC) producing 4'-phosphopantetheine. Finally, the bifunctional 4'-phosphopantetheine adenylyltransferase/dephospho-CoA kinase (COASY) attaches the adenylyl group and phosphorylates 4'-phosphopantetheine, yielding the product CoA. In a reverse hypothetical scheme, CoA is processed by either single or combined actions of acid phosphatases (ACP), nudix hydrolases (NUDT), and nucleotide pyrophosphatases (ENPP) to form pantetheine, which is further degraded to pantothenate by pantetheinases or vanins (VNN). Thirdly, the utilization of CoA to form acyl-CoA, protein bound or mixed thiol disulfides contributes in CoA levels and its homeostasis inside the cells. From: Srinivasan, B. Rerouting 'coenzyme A' biosynthesis [Groningen]: University of Groningen. (30).

The D enantiomer of B5 is the only form used in all biologic pathways, including bacterial pathways, and it is the only form recognized by the human Sodium Multiple Vitamin Transporter (NaMVT) which actively transports B5, biotin and alpha lipoic acid in from the gut. (33-36) The same NaMVT also transports B5 from the blood into the brain at the choroid plexus. (37) It appears that our source of B5 is produced by specific intestinal bacteria either de novo or from the CoA in the diet. (23, 30, 32) This suggests that a change in the bacterial species that make up the microbiome may bring with it unexpected B vitamin deficiencies, that are completely unrelated to food intake.

Pantothenic Acid Body Stores:

The original vitamin D study population showed improvement in sleep for two years. The sleep issues and pain that returned after two years resolved rapidly with B5 supplementation. This suggested that D supplementation had somehow induced a B5 deficiency state without a change in diet, by changing the B5 demand, producing a mismatch of supply to demand, or by the slow depletion of body stores. Despite the claim that water soluble vitamins are not stored there are two studies confirming the idea that there are indeed, B5 body stores. (38,39) Large doses of B5 produced delayed increases in urinary excretion after several days of supplementation, with little change in the blood level. This implies that the evaluation of a "vitamin deficiency" is not a simple blood level, at least for B5. Also, if the intention of better sleep is better body repair then the B vitamins could certainly be considered the building blocks of those repairs and better sleep might result in a higher rate of use. It is hypothesized that increased use of B5, in combination with reduced intestinal B5 production led to an eventual depletion of body stores and delayed symptoms of B5 deficiency.

Are Probiotics the Answer?

The foursome of normal bacterial species making up the healthy human microbiome have been shown to appear spontaneously in normal babies by 3 months of age and are then self-sustaining until old age. (40) The use of probiotics is a very recent trend that has so far proven to be unsuccessful at re-creating self-sustaining normal cultures. Thus, the key to returning the microbiome to normal is not the *supply* of bacteria, but recreating the *intestinal environment* that favors the healthy foursome. It's likely that those 4 species create a "B vitamin soup" that specifically promotes their growth, and probably inhibits others. They are supplying important growth factors to the bacteria as well as the cells that line the GI tract and many of the immune



system cells that are known to play a very important role in antigen recognition. (8,9) Based on the observed response to a combination of D plus B50 in over 5000 patients there are small amounts of the health-promoting four species still present in the GI tract. One need only provide the proper environment using D and B50 and those species will grow back to become the predominant foursome again.

Are Antibiotics the Cause?

The exact beginning of the epidemic of the “wrong microbiome” is hard to establish but one could use the emergence of the term “irritable bowel syndrome” (IBS) as an approximation. Though the wider use of antibiotics has been blamed for this change in bacterial species, there were two generations who used antibiotics between WW II and the mid 1980’s, without long-term, deleterious GI results. The emergence of IBS seems to be more closely linked to vitamin D deficiency which began in the 1980’s with the advent of sunscreen and air-conditioning. Given the documented seasonal variations in microbial populations of bear feces (41) and the idea that vitamin D might convey that seasonal effect, it is certainly tempting to ascribe the epidemic of IBS and the “wrong” microbiome to the parallel rise in D deficiency. (26) The fact that only 2% of the >200 species of normal GI tract bacteria have ever been grown outside the body suggests an obvious lack of knowledge regarding bacterial growth factors.(23,24,40) It appears that vitamin D has never been considered as a possible bacterial growth factor. This, despite the fact that the original beer and bread cultures referred to above are a symbiotic mixture of yeast providing vitamin D2 and bacteria providing B vitamins.

The 8-Pack of B Vitamins:

The B vitamins are very biologically intertwined in their gut production, their intermediary steps and their final roles in the cell. (42) This implies that patients with an abnormal microbiome should be supplemented with all 8 and they are probably never deficient in just one B. We may be seeing symptom complexes that are actually a result of several concomitant deficiencies. It is pertinent that there are reports of burning, small fiber-type neuropathy symptoms induced by overdose with pyridoxine (B6) suggesting that B5 and B6 may overlap somewhat in clinical symptoms and that pushing the dose of one B might, under certain circumstances, induce deficiency in a second. (43) Thus the habit of supplementing individual B’s, such as thiamine alone in alcoholics, based on a thiamine blood level, or supplementing two or three individual B’s for dementia or mood disorders should be carefully re-evaluated.

Pantothenic Acid Autoimmunity and Pain:

Pantothenic acid is used to make CoA which is a cofactor in over 100 processes in the body. (30, 44,45) Changes in the microbiome are felt to be directly linked to the increased incidence of autoimmunity. (46,47) Based on the patient populations reported above, several years of sustained vitamin D deficiency < 30 ng/ml consistently produces an abnormal microbiome, even in those without IBS symptoms. These combined deficiencies have resulted in epidemics of “fibromyalgia” and burning “neuropathic pain” accompanied by insomnia, OSA, and chronic fatigue. Inappropriate movements in sleep produce pain and stiffness on awakening or joint deterioration. Changes in the



microbiome and the accompanying vitamin deficiencies produce immune system abnormalities that predispose to autoimmune disease. This may mean that the majority of non-traumatic pain currently being treated with narcotics is the result of a combined vitamin deficiency disorder that could be cheaply and effectively treated once recognized as such.

Pantothenic Acid and Acetylcholine:

Acetylcholine (ACh) is one of the neurotransmitters responsible for normal transitions between sleep phases as well as paralysis during deep sleep. The parasympathetic side of the autonomic nervous system, which uses ACh exclusively, plays a very large role in normal sleep. (48,49) CoA is the cofactor used to produce ACh therefore it seems likely that the B5-induced agitation and insomnia described above were through actions of ACh. The immediate response to the 400 mg dose of B5 may suggest that B5 is the rate limiting step for ACh production in some areas of the brain under certain circumstances. The finding that D produces expression of Choline Acetyltransferase in the NRPOC may explain the apparent synergistic effect produced by a D blood level of 60-80 plus B5. ACh is known to control both alertness during the day, acting on nicotinic receptors in specific frontal areas, and sleep at night.(48) This might suggest a shared etiology for the epidemic of attention deficit disorder and sleep disorders which have both occurred over the last 40 years. (50)

Cholinergic dysfunction is now thought to play a major role in the etiology of Parkinson's disease, cerebellar degeneration syndromes and Alzheimer's disease. (51-53) Cholinergic imaging techniques demonstrate very early involvement of specific cholinergic systems in Parkinson's disease and in cerebellar degeneration syndromes. (51) There are also specific balance issues in Parkinson's that are more closely tied to cholinergic dysfunction by anatomic and imaging studies than to lack of dopamine. (51)

REM behavioral disorder and B5:

REM behavioral disorder (RBD), the aggressive acting out of dreams, is thought to presage the development of Parkinson's disease. It is thought to be early cholinergic dysfunction, starting years before changes in dopamine levels produce Parkinsonian signs. (51) An accidental cure of RBD with B50 led to a successful uncontrolled trial of small dose B5 in nine patients with RBD. The usual regimen of D plus B50 resulted in complete resolution of RBD in all patients. B50 was stopped after month three and the RBD usually recurred in month 4 or 5. B5 was then titrated up, nightly, in 5 mg increments (in small dose B complex) until there was no acting out. The doses have ranged from 35 mg to 65 mg but are extremely specific, a 5 mg increase above the successful dose producing RBD again, and the sustained effect is dependent on maintaining a D blood level of 60-80ng/ ml as well. (unpublished personal observation)

The presenting complaint of several of these patients was narcolepsy, or the overwhelming inability to stay awake during the day, not RBD. Frequently RBD has been present in the background for years but is the complaint of the spouse, and therefore not mentioned in the history. It is unclear how long patients need to stay on the above described additional B's. If our sleep biology was



formed around the minute to minute intestinal supply of the B vitamins then an extra supply should be necessary for only a finite period of time until deferred repairs are completed.

Pantothenate kinase neurodegeneration :

A more specific example connecting B5 deficiency to Parkinson's disease is the autosomal recessive genetic disorder pantothenate kinase-associated neurodegeneration (PKAN). A mutation in Pantothenate Kinase 2, which interrupts the conversion of B5 to CoA in the brain, causes neurodegeneration in childhood, with dystonia and spasticity. (52) The same mutation can also present as Parkinson's disease in adults. (52) This probably suggests that there are milder disorders affecting the conversion of B5 to CoA that are completely without effect until the B5 supply from the microbiome becomes reduced due to vitamin D deficiency. As we age we make less D per hour of sun exposure, suggesting that an abnormal microbiome was always part of what we've called "normal aging". D deficiency, abnormal microbiome and resulting B vitamin deficiencies have probably always been part of the underlying pathophysiology of the common degenerative neurologic illnesses such as Alzheimer's and Parkinson's disease.

Heart Rate Variability Studies, Parasympathetic Nervous System and B5 Deficiency:

ACh is the neurotransmitter of the parasympathetic half of the autonomic nervous system, known by the moniker of "rest and digest". If vitamin D deficiency has no effect on the adrenergic supply, but focally affects the supply of ACh one would expect to be able to document a parallel increase sympathetic tone. Heart Rate Variability (HRV) measurements over the last ten years have documented exactly that ; inappropriately elevated sympathetic tone in numerous disorders associated with sleep issues and an abnormal microbiome. (54-57) We have assumed that the sleep interruption itself causes this "stress reaction", but it is equally possible that low ACh results in unopposed adrenergic "fight-flight" that is unmatched by ACh "rest and digest". The lack of normal sleep resulting from lack of ACh makes for a self- perpetuating downward spiral of more and more "stress".

Futher Study of B5 and Acetylcholine:

Having said that CoA is responsible for 100 processes in the body it's important to note that there were very specific symptoms noted by participants of this D/B50 trial: sleep issues and pain related to abnormal paralysis in sleep. Those effects were very rapid and very dose dependent. I have made an argument that they are happening specifically in the sleep switches. There is clearly a synergistic effect in the brainstem sleep nuclei between vitamin D and B5 that probably relates to their roles in the supply of ACh. These observations suggest further areas of study regarding the synthesis of CoA in different parts of the brain, as well as different synthetic pathways for ACh. ACh is a neurotransmitter that is used in many parts of the body; the neuromuscular junction, the sympathetic ganglia, the adrenal gland. The idea that there might be an immediate, focal increase in supply of ACh in only specific brain areas, brought on by B5 supplementation, is very unexpected and deserves further study as well.



Vitamin D:

Vitamin D has a very contentious history and is still only partially understood. There are many competing theories about its “purpose” but the assertions that it has only one action; bone metabolism, only one active form; D 1,25 OH, and only one receptor; the nuclear vitamin D receptor are both antiquated and potentially dangerous. D has many, many actions. It has several “active forms” that do not act on the nuclear vitamin D receptor. (58-67) There are probably active forms that are still undiscovered. The one area where there is widespread agreement is that the use of sunscreen and air conditioning has produced a world-wide epidemic of D deficiency. (6) So, we are left supplementing this hormone with a woefully incomplete understanding of it.

D is a hormone therefore its clinical effects are based on blood level, not dose. Each vitamin D expert has their own “ideal D blood level” but, in fact, we still do not know what the *ideal* D level is for humans. As there are hundreds of effects, across numerous organ systems, it would be nice if those effects could be separately queried. To some extent that is what is accomplished by studying D in single cell preparations and, in fact, there may be different “ideal” blood levels for different body effects. Sleep effects were easily observed by just asking patients about their sleep, yet few clinical trials make mention of how the participants *feel* upon achieving a certain blood level, let alone sustaining a blood level over time. Also, the apparent clinical effect on sleep was tied to the D3 25OH level, not the D3 1,25 OH level suggesting that D3 25OH may be an active form of D, at least in the brain. There is a recent report of an independent, cytosolic effect of D3 25OH supporting this idea (67)

Vitamin D Clinical Trials:

We have just started to see clinical trials done appropriately by dividing the D blood levels of cases and controls into quintiles and comparing the clinical effects within and across quintiles. But most human trials still give a specific dose and compare averaged blood levels of cases to averaged levels of controls. When we achieve an *averaged* change in blood level without a “significant” clinical effect across participants we incorrectly presume a lack of effect. If D has its major effect by encouraging normal sleep, and therefore hundreds of body repairs, one would not expect to see the impressive single-cell effects of vitamin D until its “ideal” level was achieved and maintained. Those confirmatory studies still need to be done.

Dosing Vitamin D Hormone

In my experience, managing over 5000 patients for more than 7 years, there is a huge dose range between individuals. Individuals with a D deficient level of 15ng/ml can require as little as 1500 IU/day or as much as 50,000 IU/day to achieve an increase in blood level of 20 ng/ml in a month. Vitamin D can be thought of as a trophic hormone and it is used by the body in hundreds of ways. Not surprisingly, the dose to sustain a fixed blood level drifts down over years. Perhaps after years of D deficiency, there is a higher “daily use” initially, as deferred repairs are made, which then slowly drifts down. Despite the fact that vitamin D was discovered over 70 years ago all current blood level recommendations and dosing recommendations are still based mostly on personal opinion, there is no profit in D3 and appropriate clinical trials are long and difficult.



Vitamin D and the Brain:

The above described “seasonal adaptation” effect of D, is just one of many layers of D’s actions throughout animal and plant biology. On a single cell level D has been linked to abnormal inflammation and inadequate cellular repair. (58-67) Vitamin D receptors ring the lateral ventricles of the brain and it is very likely that it plays an important role in the maintenance of the blood brain and blood nerve barrier. (4,5) There are many D receptors in the placenta suggesting a role in the immune protection of the fetus. (69) Vitamin D has been shown to play numerous roles in the gut, even absent the above described theories regarding D and the microbiome. (58-60,62,66,67) The heterodimer arrangement of the vitamin D receptor allows D to pair up with several different partners to have many of different effects in different organs and it’s likely that this will be the case in the brain as well. The direct effects of D on the brain are just beginning to get the attention they deserve. (70-80)

Aging should not be viewed as an inevitable, age-related decline in function. The triad of D deficiency, abnormal microbiome and resultant B deficiencies has always been there, behind the scenes, of what we’ve called “normal aging”. Hair thinning, loss of teeth, memory decline, balance difficulties, morning stiffness, constipation, and sleep issues have all been common in the elderly, but they are not inevitable. They have specific biochemical mechanisms. Acquiring a better understanding of this cascade of events provides an opportunity to reverse normal aging. But successful prevention or reversal of age-related brain disease ultimately depends on a better understanding of the real miracle: normal sleep.



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