How to Fix your Sleep

Updates and Improvements

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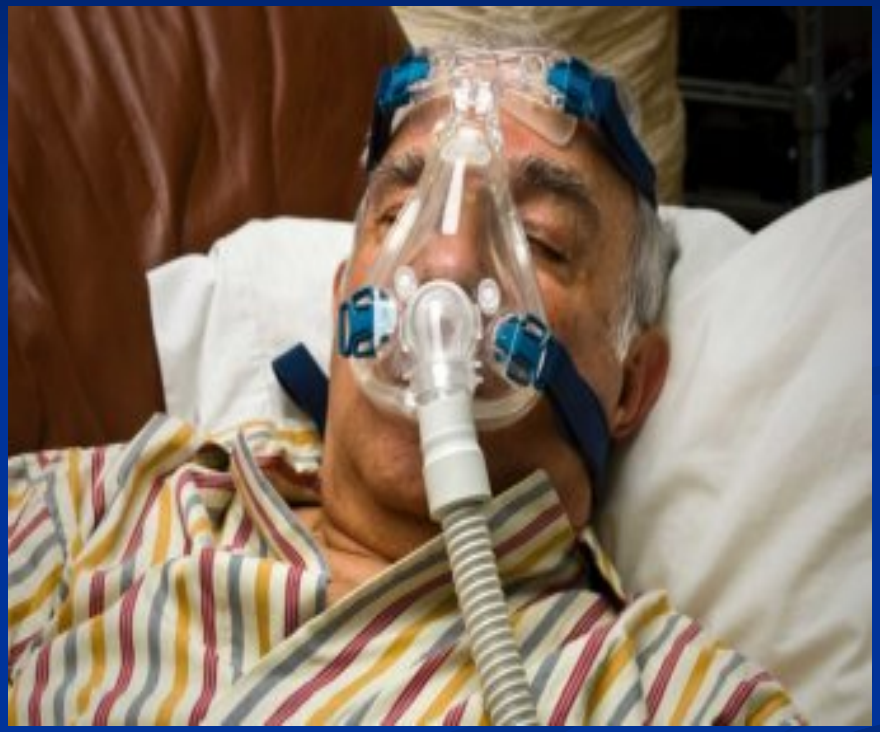
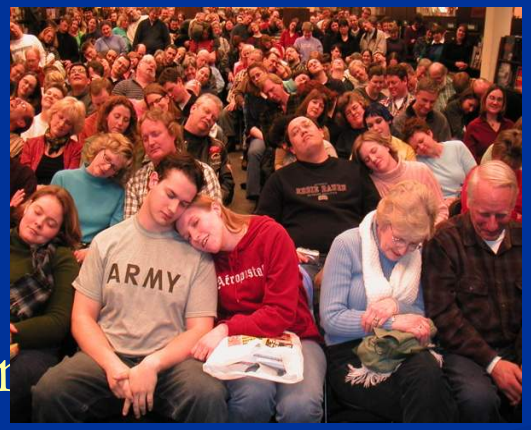
Sleep Apnea

- After bypass surgery some of the fat guys stopped breathing in their sleep even while propped up in the ICU bed.
- The ICU nurse, of course, called the pulmonologist and the CPAP mask was born.
- And we were told it was just fat guys.
- Sleep apnea is just the tip of the iceberg and may represent end stage disease, after 20-30 years of abnormal sleep.



Sleep disorders

- In the last 40 years sleep disorders have become epidemic around the world
- Where electricity has arrived so have sleep disorders.
- Why?
- And why is it ir



Sleep Apnea and Cardiac Dz

Cardiovasc Psychiatry Neurol. 2014;2014:631380.

Correlation between Obstructive Sleep Apnea Syndrome and Cardiac Disease Severity.

Javadi HR1, Jalilolghadr S2, Yazdi Z3, Rezaie Majd Z1.

Background. Obstructive sleep apnea (OSA) syndrome is one of the most common respiratory disorders in humans. There is emerging evidence linking OSA to vascular disease, particularly hypertension. The underlying pathophysiological mechanisms that link OSA to cardiovascular diseases such as hypertension, congestive heart failure, and atrial fibrillation are not entirely understood. The aim of this study was to investigate the association of obstructive sleep apnea hypopnea syndrome (OSAHS) with coronary atherosclerotic disease (CAD). Methods. A questionnaire survey based on Berlin questionnaire and Epworth Sleepiness Scale (ESS) was conducted among 406 patients to assess demographic data and the symptoms, such as excessive daytime sleepiness and snoring. Epworth Sleepiness Scale and Berlin questionnaire were completed by all of the patients. Venous blood samples were obtained for biochemical tests. Characteristics of coronary arteries were collected from angiographies' reports. All patients were divided into two groups based on results from Berlin questionnaire: low risk patients for OSA and high risk patients for OSA. Data were analyzed by SPSS software version 13. Results. Mean age of patients was 61.8 ± 10.5. 212 (52.2%) patients were categorized as high risk group for apnea. Also, excessive daytime sleepiness was reported in 186 patients (45.8%). **The severity of coronary artery involvement, daytime sleepiness, and electrocardiogram abnormalities was significantly higher in high risk patients for OSA compared with low risk patients. High risk patients had higher level of FBS and LDL and lower level of HDL cholesterol ($P < 0.05$)**.

CONCLUSIONS:

Our study found a strong correlation between the number of stenotic vessels and OSA. Based on our findings, OSA can be a predisposing factor for cardiac diseases.

Sleep Apnea and Heart Dz HTN

Chest. 2014 Jul;146(1):66-72.

OSA is common and independently associated with hypertension and increased arterial stiffness in consecutive perimenopausal women. Pedrosa RP, Barros IM, Drager LF, Bittencourt MS, Medeiros AK, Carvalho LL, Lustosa TC, Carvalho MM, Ferreira MN, Lorenzi-Filho G, Costa LO

BACKGROUND:

Perimenopause is associated with increased cardiovascular risk. OSA is an emerging risk factor for cardiovascular disease, particularly among men, but the independent contribution of OSA to cardiovascular risk in climacteric women is not clear.

METHODS:

We evaluated 277 consecutive women (age, 56 [52-61] years; BMI, 28 [25-32] kg/m2) without manifest cardiovascular disease (heart failure, coronary disease, or stroke). All women underwent 24-h ambulatory BP monitoring, arterial stiffness evaluation (pulse wave velocity), and portable sleep study.

RESULTS:

OSA (apnea-hypopnea index ≥ 5 events/h) and moderate to severe OSA (apnea-hypopnea index ≥ 15 events/h) were diagnosed in 111 (40.1%) and 31 (11.1%) women, respectively. None of the participants had received a previous diagnosis of OSA. Women with moderate to severe OSA vs those without OSA had a higher prevalence of hypertension, were prescribed more medications for hypertension, had higher awake BP (systolic, 133 [125-142] vs 126 [119-134] mm Hg [P < .01]; diastolic, 82 [78-88] vs 79 [74-85] mm Hg [P = .07]), higher nocturnal BP (systolic, 125 [118-135] vs 115 [109-124] mm Hg [P < .01]; diastolic, 73 [69-79] vs 69 [62-75] mm Hg [P < .01]), and more arterial stiffness (pulse wave velocity, 11.5 [10.1-12.3] m/s vs 9.5 [8.6-10.8] m/s, P < .001). Oxygen desaturation index during the night was independently associated with 24-h arterial BP and arterial stiffness (per five-unit increase in oxygen desaturation index, β = 1.30 [95% CI, 0.02-2.54; P = .04] vs 0.22 [95% CI, 0.03-0.40; P = .02] in women with vs without OSA, respectively).

CONCLUSIONS:

OSA is common, underdiagnosed, and independently associated with high BP and increased arterial stiffness in perimenopausal women.

Sleep Apnea and cholesterol

J Clin Sleep Med. 2014 May 15;10(5):475-89.

Effect of obstructive sleep apnea hypopnea syndrome on lipid profile: a meta-regression analysis.

Nadeem R1, Singh M2, Nida M3, Waheed I1, Khan A1, Ahmed S4, Naseem J5, Champeau D1.

BACKGROUND:

Obstructive sleep apnea (OSA) is associated with obesity, metabolic syndrome, and dyslipidemia, which may be related to decrease androgen levels found in OSA patients. Dyslipidemia may contribute to atherosclerosis leading to increasing risk of heart disease.

METHODS:

Systematic review was conducted using PubMed and Cochrane library by utilizing different combinations of key words; sleep apnea, obstructive sleep apnea, serum lipids, dyslipidemia, cholesterol, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglyceride (TG). Inclusion criteria were: English articles, and studies with adult population in 2 groups of patients (patients with OSA and without OSA). A total 96 studies were reviewed for inclusion, with 25 studies pooled for analysis.

RESULTS:

Sixty-four studies were pooled for analysis; since some studies have more than one dataset, there were 107 datasets with 18,116 patients pooled for meta-analysis. All studies measured serum lipids. Total cholesterol pooled standardized difference in means was 0.267 ($p = 0.001$). LDL cholesterol pooled standardized difference in means was 0.296 ($p = 0.001$). HDL cholesterol pooled standardized difference in means was -0.433 ($p = 0.001$). Triglyceride pooled standardized difference in means was 0.603 ($p = 0.001$). Meta-regression for age, BMI, and AHI showed that age has significant effect for TC, LDL, and HDL. BMI had significant effect for LDL and HDL, while AHI had significant effect for LDL and TG.

CONCLUSION:

Patients with OSA appear to have increased dyslipidemia (high total cholesterol, LDL, TG, and low HDL).

Sleep Apnea and Atrial Fibrillation

Acta Cardiol. 2014 Jun;69(3):291-6.

Occurrence of poor sleep quality in atrial fibrillation patients according to the EHRA score.

Szymanski FM, Filipiak KJ, Karpinski G, Platek AE, Opolski G.

BACKGROUND:

Atrial fibrillation (AF) is the most common arrhythmia that affects the quality of life by causing deleterious health consequences, and impairing sleep quality. The severity of AF symptoms may range from very mild to the very intense which can be assessed by the European Heart Rhythm Association (EHRA) score. The aim of the study was to assess the prevalence of poor sleep quality in AF patients, in relation to the symptom severity based on the EHRA score.

METHODS:

177 consecutive patients, hospitalized between 2011 and 2013 with non-valvular AF and no history of myocardial infarction, stroke or decompensation of heart failure within the last 6 months, were enrolled into the study. Sleep quality was assessed by the Pittsburg Sleep Quality Index (PSQI) in all patients at admission. Medical history and data concerning AF symptoms and severity by the EHRA score were gathered by a qualified physician.

RESULTS:

Poor sleep quality was present in 49.7% of patients. Patients with poor sleep quality were more often females (66.6% vs. 35.8%; P = 0.007), were older (57.9 +/- 10.1 vs. 53.9 +/- 10.0 years; P = 0.005), and had higher systolic blood pressures (134.4 +/- 16.4 vs. 129.8 +/- 17.8 mmHg; P = 0.03). Poor sleep quality was present in 33.3% of the EHRA I group, 43.9% of the EHRA II group, 58.1% of the EHRA III group, and 61.5% of the EHRA IV group (p value for trend 0.01).

CONCLUSIONS:

Poor sleep quality is highly prevalent in AF patients, affecting approximately half of them. It is related to the severity of symptoms, and prevalence rises with every degree of the EHRA score.

Sleep and Heart Disease

PLoS One. 2014 Aug 5;9(8):e104324. doi: 10.1371

Complaints of sleep disturbances are associated with cardiovascular disease: results from the Gutenberg Health Study.

Michal M1, Wiltink J2, Kirschner Y3, Schneider A4, Wild PS5, Münzel T6, Blettner M4, Schulz A6, Lackner K7, Pfeiffer N8, Blankenberg S9, Tschan R2, Tuin I2, Beutel ME2.

BACKGROUND:

Despite their high prevalence, sleep disorders often remain unrecognized and untreated because of barriers to assessment and management. The aims of the present study were to examine associations of complaints of sleep disturbances with cardiovascular disease, related risk factors, and inflammation in the community and to determine the contribution of sleep disturbances to self-perceived physical health.

METHOD:

The sample consists of n=10.000 participants, aged 35 to 74 years . A population based community sample in Germany. Cross-sectional associations of complaints of sleep disturbances with cardiovascular risk factors and disease, biomarkers of inflammation, depression, anxiety, and physical health status were analyzed.

RESULTS:

19% of our sample endorsed clinically significant sleep disturbances. In the unadjusted analyses severity of sleep disturbances increased with female sex, low socioeconomic status, living without a partnership, cardiovascular disease, depression, anxiety, poor physical health, increased levels of C-reactive protein and fibrinogen. After multivariate adjustment robust associations with coronary heart disease, myocardial infarction and dyslipidemia remained. Complaints of sleep disturbances were strong and independent contributors to self-perceived poor physical health beyond depression, anxiety and medical disease burden.

CONCLUSIONS:

Given the high prevalence of complaints of sleep disturbances and their strong impact on health status, increased efforts should be undertaken for their identification and treatment.

Sleep Apnea and Stroke and MI

J Intern Med. 2014 Dec;276(6):659-66. doi: 10.1111/joim.12302. Epub 2014 Sep 17.

Cardiovascular risk in patients with sleep apnoea with or without continuous positive airway pressure therapy: follow-up of 4.5 million Danish adults. Lamberts M1, Nielsen OW, Lip GY, Ruwald MH, Christiansen CB, Kristensen SL, Torp-Pedersen C, Hansen ML, Gislason GH.

BACKGROUND:

The prognostic significance of age and continuous positive airway pressure (CPAP) therapy on cardiovascular disease in patients with sleep apnoea has not been assessed previously.

METHODS:

Using nationwide databases, the entire Danish population was followed from 2000 until 2011. First-time sleep apnoea diagnoses and use of CPAP therapy were determined. Incidence rate ratios (IRRs) of ischaemic stroke and myocardial infarction (MI) were analysed using Poisson regression models.

RESULTS:

Amongst 4.5 million individuals included in the study, 33 274 developed sleep apnoea (mean age 53, 79% men) of whom 44% received persistent CPAP therapy. Median time to initiation of CPAP therapy was 88 days (interquartile range 34-346). Patients with sleep apnoea had more comorbidities compared to the general population. Crude rates of MI and ischaemic stroke were increased for sleep apnoea patients (5.4 and 3.6 events per 1000 person-years compared to 4.0 and 3.0 in the general population, respectively). Relative to the general population, risk of MI [IRR 1.71, 95% confidence interval (CI) 1.57-1.86] and ischaemic stroke (IRR 1.50, 95% CI 1.35-1.66) was significantly increased in patients with sleep apnoea, in particular in patients younger than 50 years (IRR 2.12, 95% CI 1.64-2.74 and IRR 2.34, 95% CI 1.77-3.10, respectively). Subsequent CPAP therapy was not associated with altered prognosis.

CONCLUSIONS:

Sleep apnea is associated with increased risk of ischaemic stroke and MI, particularly in patients younger than 50 years of age. CPAP therapy was not associated with a reduced rate of stroke or MI.

CPAP is a patch not a cure

- *If* sleep disorders are not just apnea but include reduced or absent deep sleep, insomnia, periodic limb movements and narcolepsy.
- *If* sleep disorders are now reported in all ages in all developed countries.
- *If* the articles relating sleep apnea to heart disease, stroke, high cholesterol, diabetes and multiple other diseases can be generalized to anyone who does not get enough deep sleep. Wouldn't we want to fix this?
- Are there other things that we haven't even thought of that are caused by inadequate sleep repair?

First Step: Vitamin D deficiency

- In 2011 first lecture given here hypothesizing that Vitamin D deficiency was the predisposing factor leading to the world wide epidemic of sleep disorders
- Feb 2015, first prospective study confirming this vitamin D hypothesis in a clinical trial.
- Unfortunately the D fix lasts only about two years, then it starts to fade, and other symptoms appear, often pain.

Prospective Actigraphic sleep study correlated to vitamin D levels

Vitamin D and Actigraphic Sleep Outcomes in Older Community-Dwelling Men: Massa J1, Stone KL2, Wei EK2, Harrison SL2, Barrett-Connor E3, Lane NE4,5, Paudel M6, Redline S7, Ancoli-Israel S8,9, Orwoll E10, Schernhammer E Sleep. 2015 Feb 1;38(2):251-7.

Among 3,048 men age 68 years or older, we measured total serum vitamin D. Objective estimates of nightly total sleep time, sleep efficiency, and wake time after sleep onset (WASO) were obtained using wrist actigraphy worn for an average of 5 consecutive 24-h periods.

RESULTS:

16.4% of this study population had low levels of vitamin D (< 20.3 ng/mL 25(OH)D). Lower serum vitamin D levels were associated with a higher odds of short (< 5 h) sleep duration, (odds ratio [OR] for the highest (≥ 40.06 ng/mL) versus lowest (< 20.3 ng/mL) quartile of 25(OH)D, 2.15; 95 % confidence interval (CI), 1.21-3.79; Ptrend = 0.004) as well as increased odds of actigraphy-measured sleep efficiency of less than 70% (OR, 1.45; 95% CI, 0.97-2.18; Ptrend = 0.004), after controlling for age, clinic, season, comorbidities, body mass index, and physical and cognitive function. Lower vitamin D levels were also associated with increased WASO in age-adjusted, but not multivariable adjusted models.

CONCLUSIONS:

Among older men, low levels of total serum 25(OH)D are associated with poorer sleep including short sleep duration and lower sleep efficiency. These findings, if confirmed by others, suggest a potential role for vitamin D in maintaining healthy sleep.

D is not the only problem

- I was really hoping the D level would be the only problem, unfortunately it's not.
- Last lecture, in 2013 I mentioned pantothenic acid.
- It seems to be as pivotal in fixing the sleep as vitamin D
- I was only willing to read about it because my patients were starting to fail again at the end of the 2nd year, the sleep was worsening and the pain was increasing.
- Two of my healthy 30-40 y/o 's with headache (already on B12) started to have burning in the hands and feet within months of each other, that can't just be coincidental.
- I started to wonder if I might be inducing a B vitamin deficiency with increased doses of D pushing the body to use more B's to make repairs. (B's were once called "the neuritic factor")

But why would they be B deficient?

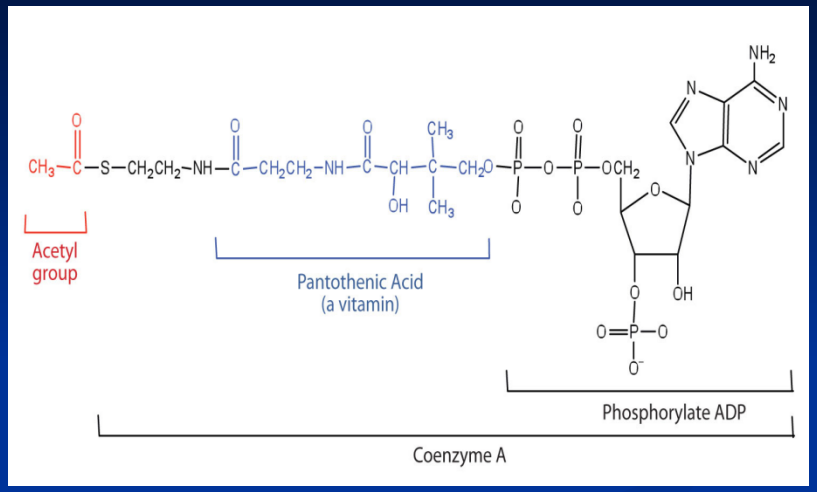
- In 2012 one of my patients brought me a book: *Overcoming the pain of inflammatory arthritis* Eisenstein P, Scheiner S. Avery Publishing 1997:
- 400 mg /day of pantothenic acid helped arthritis and **helped the sleep!**
- **Then I went to the references:**
- Pantothenic Deficiency in Man: Hodges , Ohlson MA, Bean WB. J Clin Invest. 1958 Nov;37(11):1642-57.
- Pantothenic acid deficiency had been studied in pigs: (by making their food deficient) they walked funny and then died of adrenal failure.
- Pantothenic Acid deficiency was very difficult to induce in man. It is in every food substance as Coenzyme A.
- They induced deficiency by using a blocker in two subjects and a component-created-diet, (not made from food), that was tube fed to inmates
- **After two weeks of pantothenic deficient diet; burning in the feet, trouble sleeping, headache, gait disorder and abdominal discomfort**.

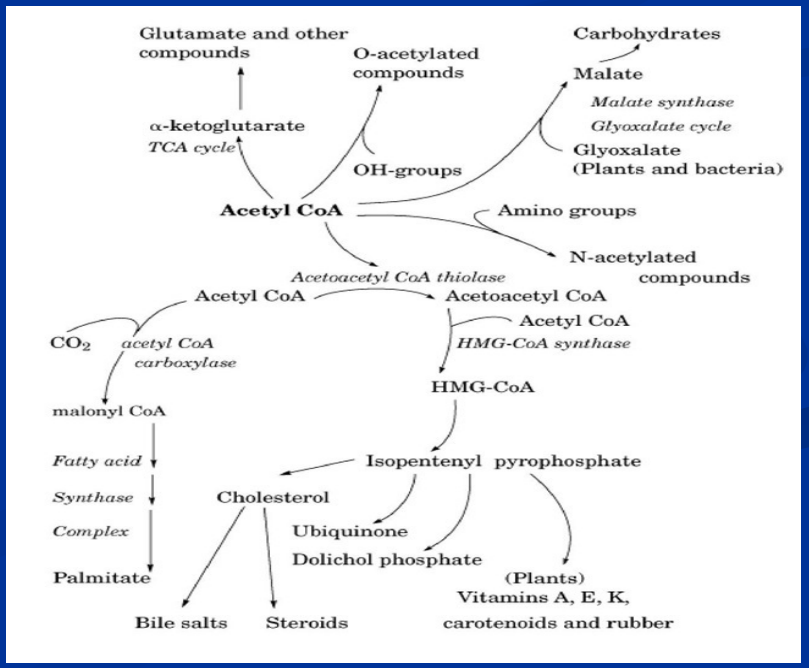
The difficulties inherent in human experimentation

- Pantothenic acid deficiency in man. Hodges RE, Ohlson MA, Bean WB J Clin Invest. 1958 Nov;37(11):1642-57.
- Experiments carried out at the Iowa State Prison on inmates who were "volunteers".
- "One of the men (No. 2) in the group designated as antagonists soon tired of it all and escaped"
- Later in 1967these same authors published articles on the pros and cons of experimentation on prisoners.
- Joint pain was not reported in these experiments
- Why would pantothenic acid supplementation help joint pain? What does pantothenic acid do?

Pantothenic Acid Makes CoEnzyme A

- CoEnzyme A below the neck makes cholesterol which then is used to make cortisol. You don't have it you can't make cortisol. This is apparently why the pigs died of adrenal failure.
- Which is why they pursued antibody response studies with and without pantothenic acid in later studies.
- This may explain the connection between sleep disorders and autoimmune disorders and pain.
- So in 2012 anyone with joint pain, normal D levels, and failing sleep got 400 mg of pantothenic acid, the dose suggested in the book.





Pantothenic Acid observations 50 years later

- In approximately 50 patients doses of 400 mg of pantothenic acid, by itself, immediately caused insomnia and agitation
- Well, it affected the sleep alright, but in the wrong direction.
- Oops there *is* a dose that is too big, I guess for this one B we don' t just urinate out the excess. What's the right dose ?
- The two patients who had developed burning in the hands and feet (two years after starting D) had immediate relief of burning in days.
- One of those two stayed on 400 mg for two more years with no apparent side effect, each time she tried to stop the burning returned.

But why would they be B deficient?

- Intestinal absorption of water soluble vitamins in health and disease. Said HM Biochem J. (2011) 437 357-372
- 7/8 B's have a *colonic bacteria source and a food source*, (we can make niacin from a tryptophan precursor)
- Did you know that we had a colonic bacterial source of B vitamins? I sure didn't.
- But that would explain how animals can hibernate for six months. They still need a daily source of B's but they don't eat.
- The bacteria eats the mucus the animal makes and provides B's in exchange, a self-sustaining biological source.
- An *Economist* article about the epidemic of wrong intestinal bacteria happened by at exactly that instant.

"The human micro-biome: Me myself, us"

The Econ-o-mist August 18, 2012

- The bacteria on and in us are commensal organisms that do things for us.
- Normal (*outside living**) animals have 4 main species: Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria.
- Fat people have the wrong bacteria. Certain bacterial species in the colon secrete short chain fatty acids that make us hungry.
- The bacteria that live inside us determine what happens to what we eat, whether it goes to fat or muscle. (So it's not my fault after all?)
- Perform a gastric bypass in a mouse, the colonic bacterial species change.
- Take that mouse's changed colonic bacteria put in a second mouse, the second mouse loses weight.
- Is this why the D deficient patients didn't lose weight even though their D's were corrected?

"The human micro-biome: Me myself, us"

The Econ-o-mist August 18, 2012

- If you have heart disease or type 2 diabetes you usually have the wrong bacteria
- If you have autoimmune diseases such as MS, type 1 diabetes, asthma, eczema you have the wrong bacteria.
- If you have had Clostridium difficil infection in the hospital you had the wrong bacteria and the right guys would have protected you from that infection.

"The human micro-biome: Me myself, us"

The Econ-o-mist August 18, 2012

- Isn't this a pretty similar population to the sleep disorders patients?
- Many of the patients I see have irritable bowel complaints as well as all the complaints they are seeing me for.
- Oddly the IBS symptoms did not resolve after two years of perfect D levels.
- Are probiotics and fecal transplant the only way to try to fix this?
- I think the low D must play a role here, the epidemics appear to have happened in parallel.

Hypothesized Low D to low B's connection

- In low D state our D supply to the intestinal bacteria goes down as we no longer have extra to pass on to them.
- Next, different bacterial species become predominant in the large intestine and we get fat and gassy and start to have more connective tissue diseases more allergies and more pain, maybe because our B levels have changed and our basal cortisol production falls.
- If 400 mg of pantothenic acid was too high how do I find out the "right" dose to help my patients sleep?
- What was the "normal dose" provided by the bacteria in a healthy host? Only the bacteria know.
- How do we get those guys to grow back?
- Lets learn about B's and bacteria

B's were the "neuritic factor"

- Early part of the 1900's :Patients had burning pain in the feet that got better with a yeast extract, they called it the "neuritic factor".
- The original studies to try to purify the "neuritic factor" showed some factors in the yeast extract were heat stable some were not and thus began the purification of chemicals that were also
- "growth factors" that were necessary for the propagation of certain bacterial species in petri dishes, these were called vitamins.

Bacterial "growth factors"

- What they found as they started to grow individual bacterial species was that one bacteria needed an outside riboflavin source but could make all the other components of metabolism.
- The next needed an outside thiamine source
- All of them probably also needed a D2 source that was made by the yeast but we didn't know about D then.
- I think our intestinal bacteria need our D supply to flourish and favor the normal foursome

How to fix the bacteria

- It turns out there are no articles supporting this idea that the normal four species need a D source.
- But it also turns out that of the thousands of species that are detected in human stool by DNA sequencing, only 2% have ever been cultured in a petri dish
- If the microbiologists never thought of providing a D source and never added it to the growth medium they never grew the species that need D.
- We know who's there by DNA sequencing but haven't looked at it in this way, it's not the supply, it's the environment, optimize their "petri dish" in our belly.

The intestinal bacteria have plenty of D now why aren't they happy?

- If the primary problem was the low D why haven't the friendly four come back now that there is plenty of D?
- If we think of it, not as a bacterial supply problem with probiotics and fecal transplant, but more as a petri dish.
- We're trying to make the colonic environment favor the friendly four. Maybe they hang out together to get B's from each other.
- Perhaps A that makes thiamine and B that makes riboflavin hang out with C and D because when they are all secreting into their surroundings they make the B's for each other.
- What if there are piles of poop in between A and B now so the B's they need are not being supplied, so what will happen when we add large doses of all 8 B's plus larger doses of D?

IBS is gone in three months

- My patients need big D doses in combination with B 50 or B100 for three months and the IBS is gone, presumably this means we've reverted back to the happy foursome.
- Theoretically it won't go bad again as long as we keep our D level up above about 40 ng/ml.
- The original change toward acquiring fat in the winter had a strong survival advantage, but it wasn't supposed to continue on indefinitely without a spring.

How to give B vitamins and why they are not necessarily "good for you"

- They are biologically very intertwined. They should never be given individually.
- Their absorption is, in fact, blocked by alcohol but alcoholics are not the only people with this problem now.
- Pantothenic Acid has a very narrow dose range , most noticeable after normalizing the intestinal bacteria.
- The dose of the pantothenic acid has to be adjusted to fit the amount of morning pain.
- Perhaps the amount of time spent in deep sleep making repairs affects the amount of these B vitamins that are needed.(REM deficit being made up may need more?)
- Perhaps the intestinal bacteria cannot respond to a need for more, perhaps they make a basal amount for a normal healthy human before they get sick.

REM behavioral disorder

- Inability to get fully paralyzed in sleep, acting out dreams . Said to be present in patients who later develop Parkinson's and in some Parkinson's patients.
- This suggests that the dopamine supply is "off" in REM phase. But two of my patients had no improvement with dopamine agonists and by accident used bigger doses of pantothenic acid 60-80 mg (in a B complex with all B's and after intestinal bacterial correction) and it immediately cleared. They and their spouses could both tell a difference in a 5mg dose. i,e. fixed at 65 but still moving a little at 60mg.

CoEnzyme A makes many things

- CoEnzyme A below the neck makes cortisol, but above the neck makes acetylcholine, a neurotransmitter that plays a role in alertness and in REM, apparently helping to paralyze us correctly in sleep.
- *The cholinergic system, EEG and sleep** "**Acetylcholine is a potent excitatory neurotransmitter, crucial for cognition and the control of alertness and arousal. ……Additionally, cholinergic projections from the basal forebrain act as a relay center for the brainstem–cortical arousal system, directly modulate cortical activity, and thus promote wakefulness or rapid-eye movement (REM) sleep**"
- Presumably this is also why big doses of pantothenic acid (400mg) caused insomnia and agitation
- This vitamin appears to have a direct, dose related response when taken as a supplement.
- Most of what is called pantothenic acid in our food is actually supplied as CoEnzyme A and it does not appear to act the same way.

*Bettina Platt, Gernot Riedel Copyright © 2011 Elsevier B.V.

Inadequate paralysis in sleep, pain on waking (fibromyalgia)

- In order to repair moving parts we have to get paralyzed correctly in deep sleep.
- Limbs that are moving or tensing inappropriately during the repair phases don't repair and can be painful on awakening.
- Muscle pain, jaw pain on awakening seems to be related to this.
- Joint pain may have an additional cortisol-related inflammatory component
- Many patients have muscle, joint and neuropathic pain probably from mixed B deficiencies that negatively affect their sleep.
- Not surprisingly we've used the sleep promoting tricyclic antidepressants to treat these patients. (fibromyalgia)

Pantothenic Acid adjustments

- Once the right bacteria are back they are contributing vitamins and the dose needs to goes down.
- After the three month mark go back down to 10 mg pantothenic acid in a multivitamin.
- Adjust the B dosing by ½ tab, 5mg of pantothenic acid (always with the other B's) until waking with no pain, perhaps those who have been sicker longer need higher doses.
- This should be a temporary supplement needed for making up the sleep deficit and should eventually taper down again.
- Normal humans once completely fixed do not need vitamins except vitamin D if they stay inside .
- Too much and too little pantothenic both cause morning pain that feels like "arthritis"

All Old People do Not have arthritis

- Arthritis means I wake stiff and in pain, I limber up take a shower get my coffee and it's gone.
- Why would we have more pain on awakening than at 10 am?
- It's so common that we think it's "normal" but there is always a mechanism
- This starts to show up when the paralysis in sleep is not normal, D deficiency can do it and so can combined B deficiency from wrong intestinal bacteria.
- Replacing D without fixing the bacteria often causes severe pain on awakening starting in the third year.

If we don't know about sleep we don't consider it as a cause of disease

But if you know what a part of the brain does normally you can bet there will be someone, somewhere that is suffering from that part malfunctioning.

Lets think of it that way to see what disorders might result.

Weird neurologic illnesses that I think are sleep disorders

Things that begin to appear when the sleep switches, themselves, don't have time to repair during sleep.

Malfunctioning sleep nuclei

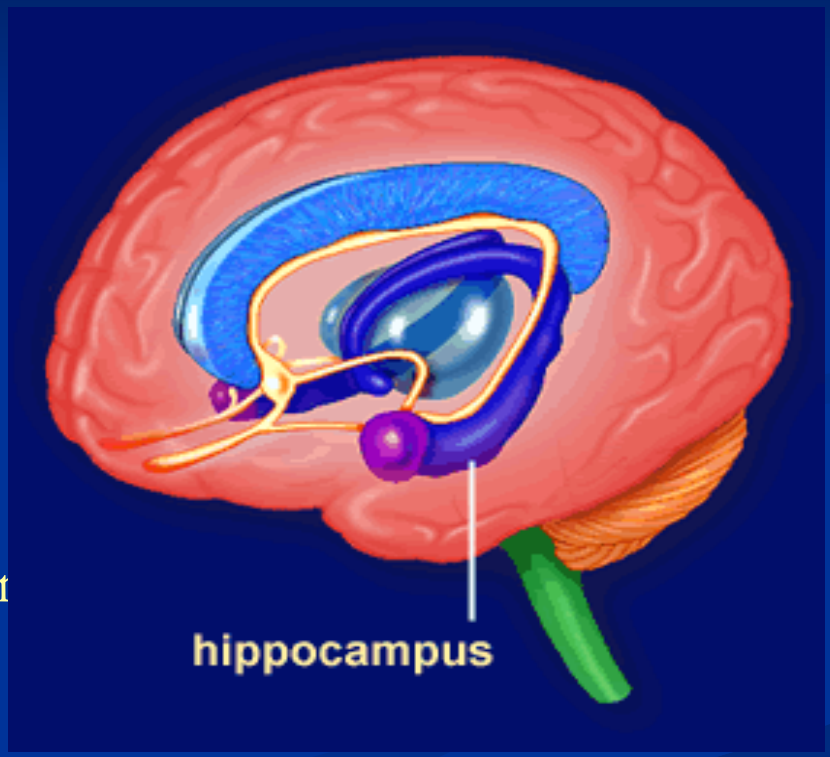
- Are there diseases that may only show up in the human population after long periods of abnormal sleep?
- Are there diseases that are just about the sleep switches, the parts of the brain that make us fall asleep, make transitions to deep sleep?
- If these switches don't have a chance to repair nightly how might they fail?

What diseases might result if the sleep switches malfunction?

- There are sleep nuclei in the brain stem, thalamus, hypothalamus, hippocampus that are only partially understood.
- But we know that they play a large role in putting us to sleep, sleep stage transitions.
- We know what the cortical EEG patterns look like while those areas are "in control" of our brain
- We know some things in animals by "lesioning" these areas.

Memory and sleep

- Sleep is the only time we don't make new memories. We "wake up" and time has passed but we don't "remember".
- Short term memory is bilateral hippocampal nuclei, analogous to the RAM memory of the computer.
- Maybe the hippocampi are "downloading" the stored information so we can't use them while that is happening
- This is not supposed to happen while we're awake, ***but what if it did?***



Transient global amnesia

- Abrupt onset of inability to make new memories.
- Patient asks the exact same question over and over.
- " Why am I at home instead of at work?"
- His wife answers, he nods as though he understands, then asks the exact same question again, with the exact same voice inflection. This may go on for 20-90 min.
- They recognize family members, they know they're not normal, they can speak, move everything.
- Often happens in the morning on awakening or after intercourse.

Transient Global Amnesia (TGA)

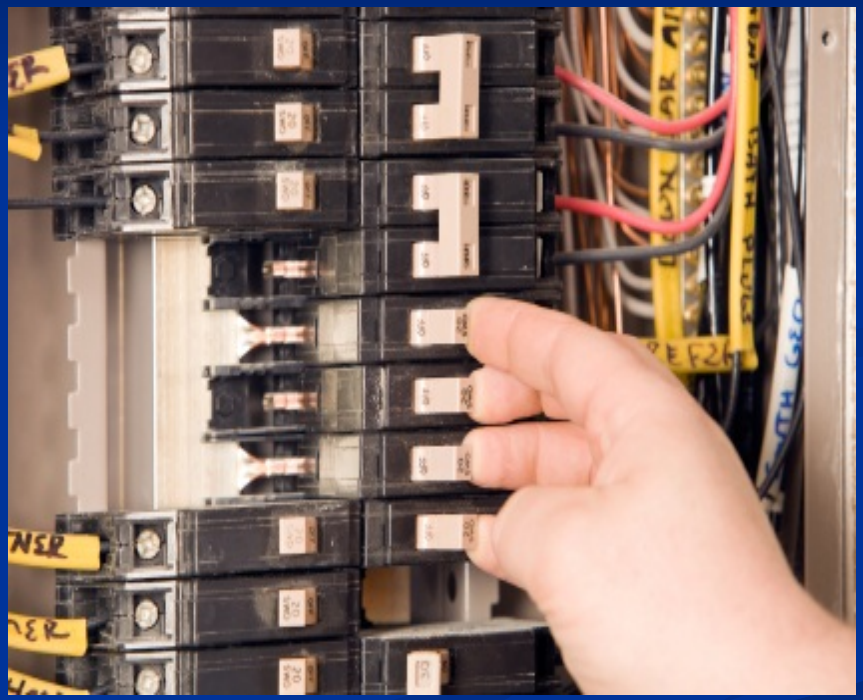
- TGA is an electrical change, a physiologic change, not an anatomic change, it is affecting both hippocampi at the same time.
- It leaves no permanent mark on the MRI, the hippocampi are in two separate vascular territories and no other part of the brain is affected, it's not a stroke.
- This is a normal event every night, the "switch" "flips" every night while we sleep, we make no new memories, but we are unconscious while it's happening.
- I think all of the patients with TGA have long standing sleep disorders, but we don't think to ask about it.

TGA is a sleep disorder

- It's uncommon, it gets better on it's own , it rarely if ever comes back.
- It is seen at times in patients with severe migraine and occasionally in patients who have strokes
- But generally it is self limiting and not associated with any other progressive brain disorder.
- The best we've done so far is "We See This" we name it, so the family can go read about it.

TGA what is the mechanism?

- ?uncoupling of a switch that is normally linked to several others including consciousness.
- Certain forms of MRI imaging do show a change in the electrical activity in the hippocampi while it's happening.
- What if we thought of every "switch" that turns on and off every night while we sleep and think of what would manifest if it "switched" while we were awake?



Sleep Anatomy

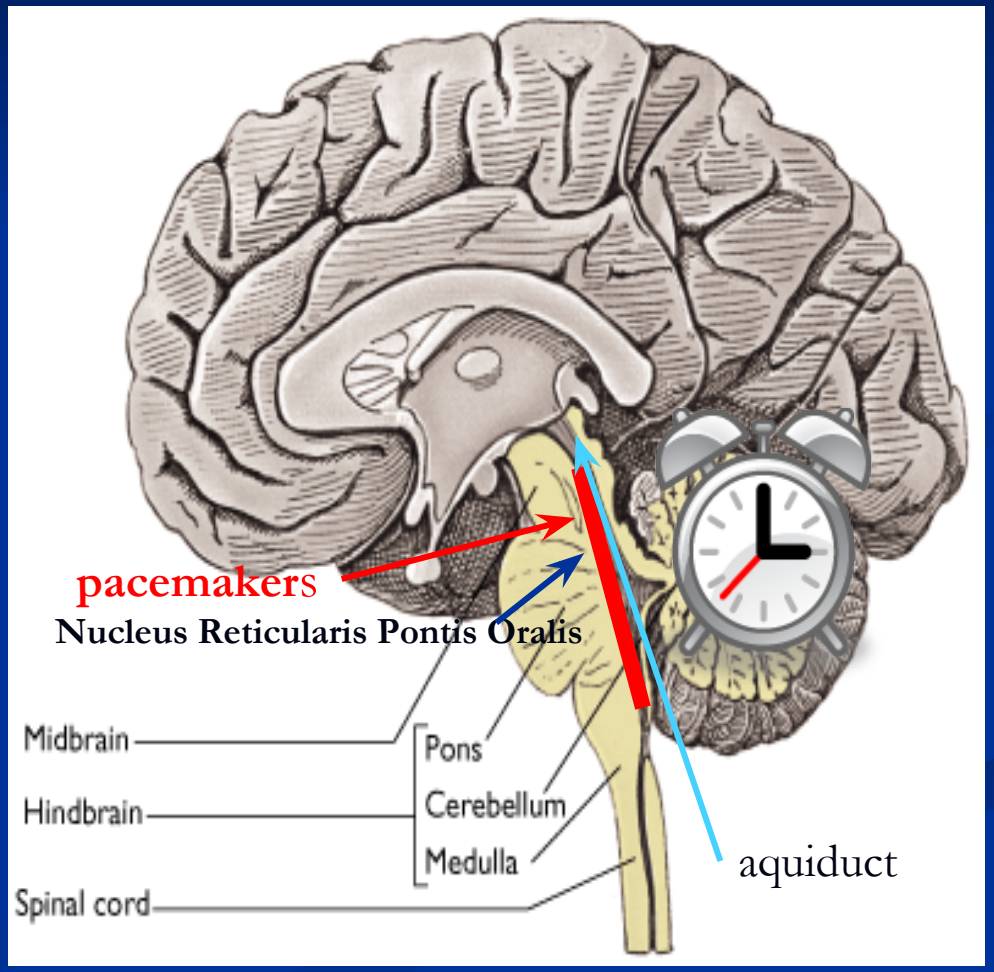
The brainstem meets the brain at a “switching station”

The Thalamus

Bilateral thalami, hypothalami and brainstem nuclei are where the sleep switches reside

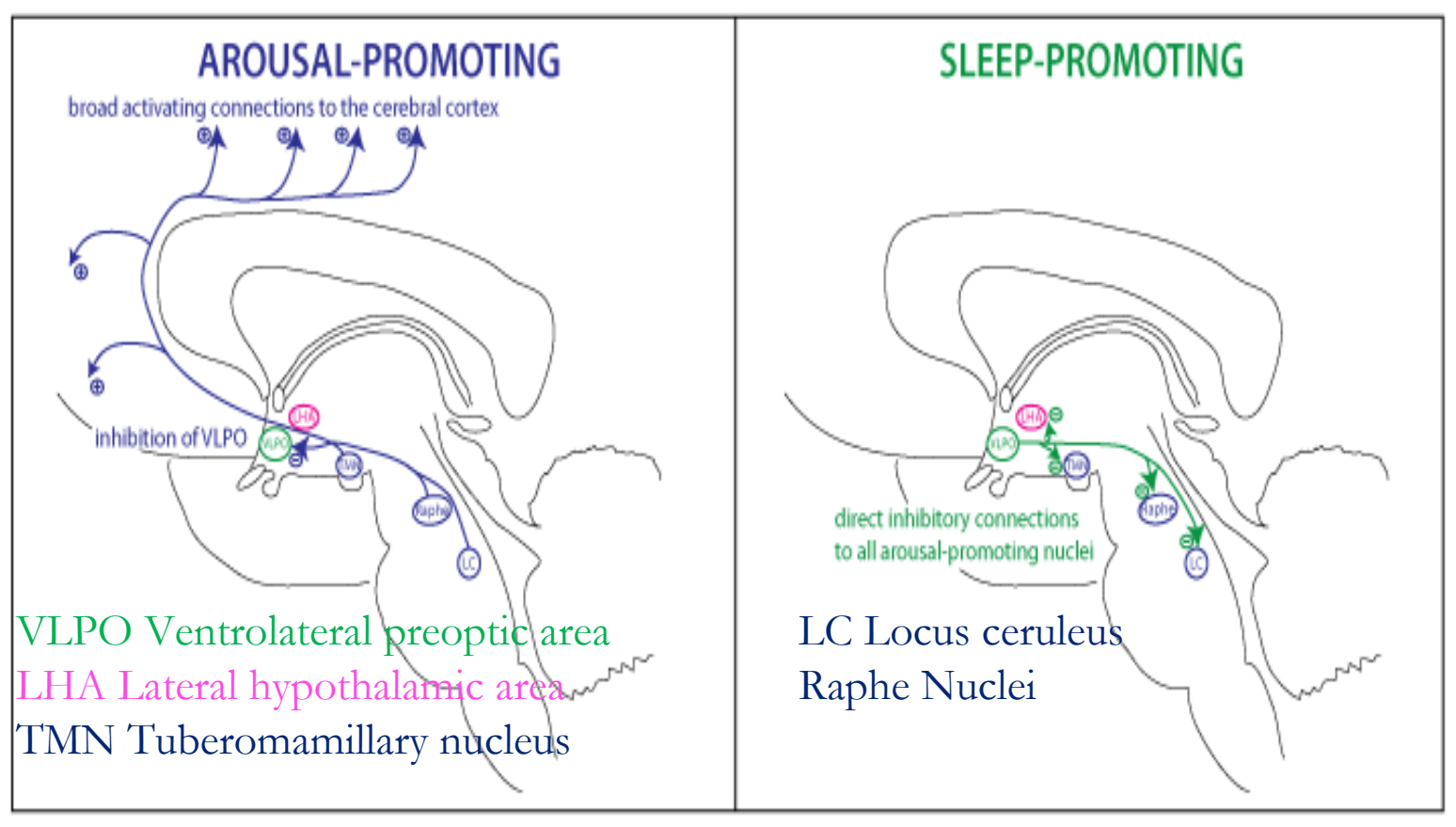
The Periaquiductal Gray runs the timing and paralysis of sleep

- The **pacemaker cells** in the periaquiductal grey beat all day all night.
- They are the brain clock that determines when we sleep
- The paralysis switch is here also, Nucleus Reticularis Pontis Oralis/ Caudalis
- The two are linked so we only get paralyzed while we are deeply asleep.
- Normal people cannot be awake and asleep at the same time.



Sleep-wake happens with a "flip- flop" switch of multiple linked nuclei

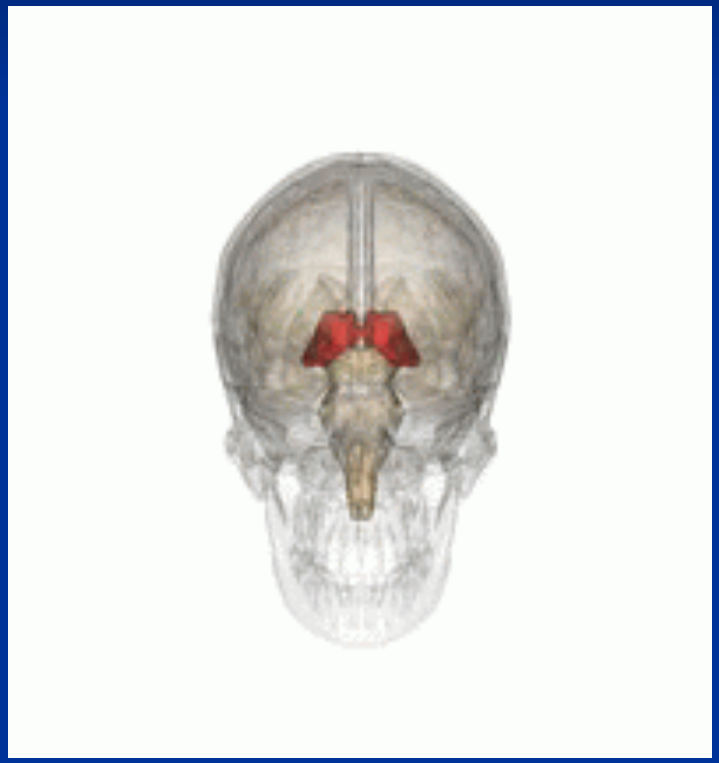
"flip flop switch" is borrowed from the software industry and refers to a system designed to guarantee that A and B can never exist at the same time.

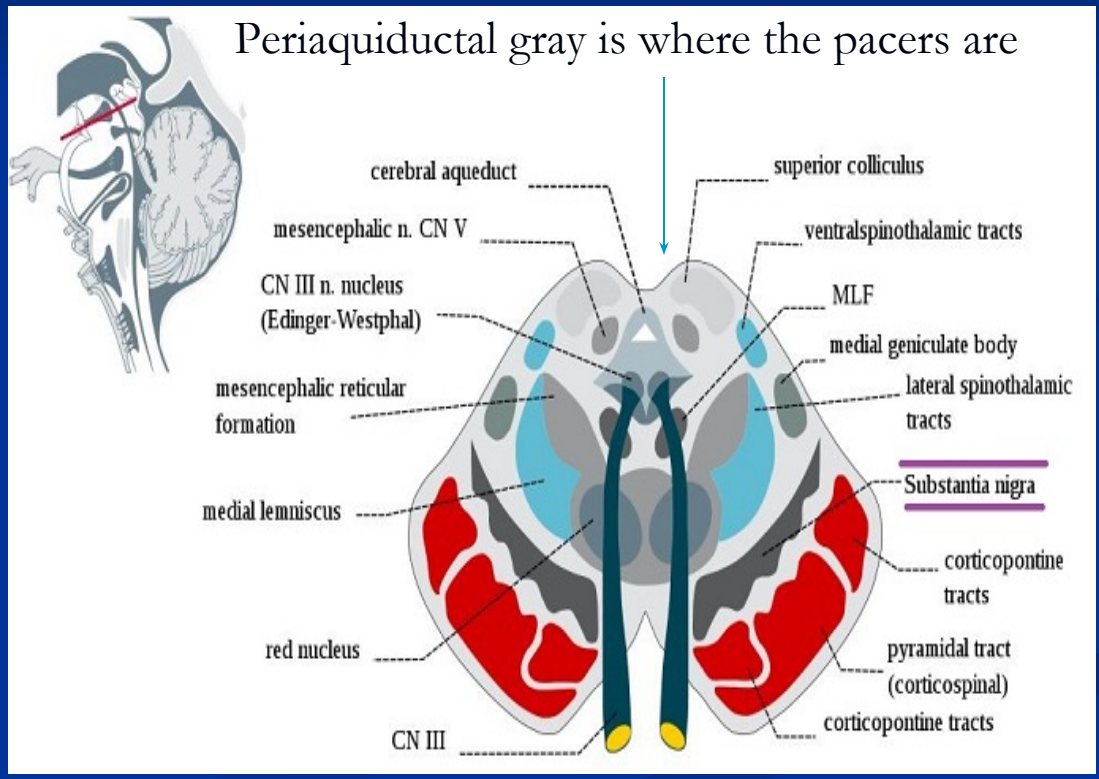


VLPO Ventrolateral preoptic area
LHA Lateral hypothalamic area
TMN Tuberomamillary nucleus

LC Locus ceruleus
Raphe Nuclei

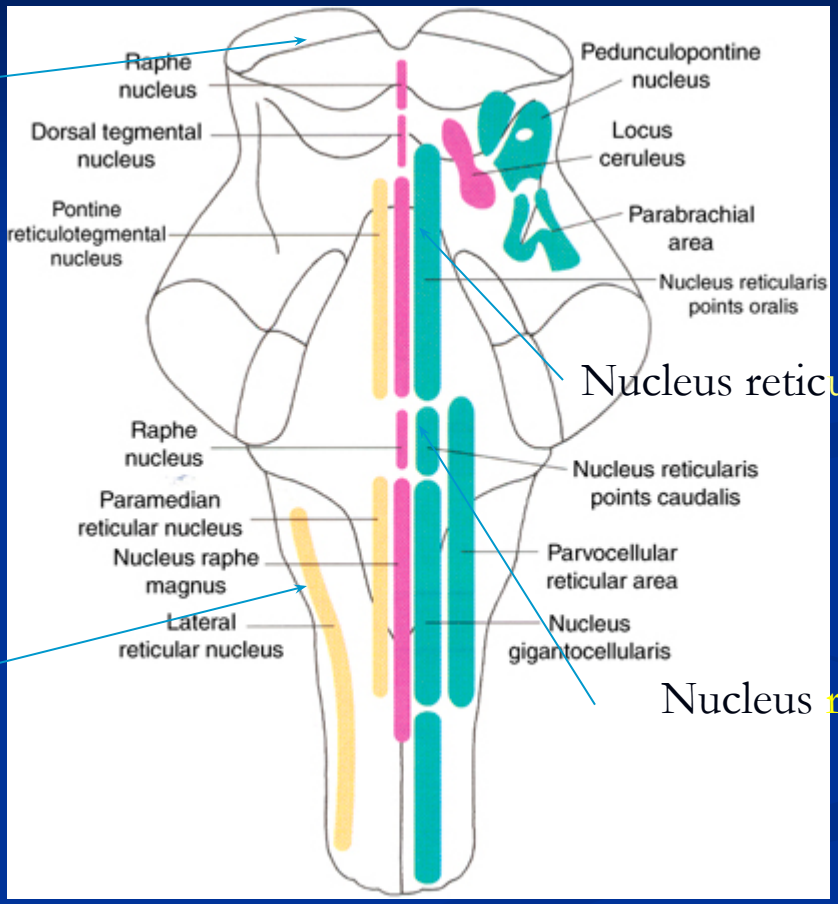
Thalamus hypothalamus brain stem and surrounding nuclei





Sleep anatomy overlaps the anatomy of "locked in" strokes

Substantia Nigra



Nucleus reticularis pontis oralis

Reticular Formation keeps us conscious

Nucleus reticularis pontis caudalis

What does "locked in" look like?

- Conscious and can hear but can't respond, can't talk, can't move.
- Is there a way that could happen spontaneously but not from stroke?
- Where the sleep paralysis switches just "flip" and "whoops" you're paralyzed.
- What would that look like? What would the patient experience?
- What tests would we do?

What do these linked switches do?

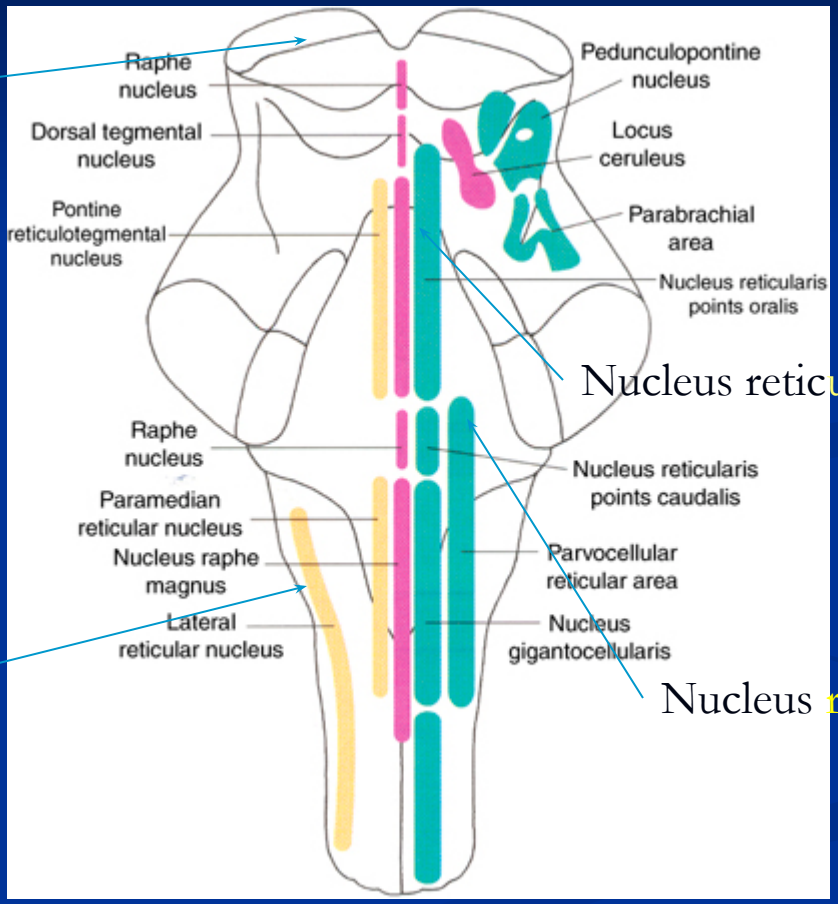
- Make us unconscious
- Turn the memory switch to another position
- Paralyze mouth/airway in such a way that we still breath and swallow but don't cry out.
- Paralyze all moving parts so repair can occur
- If there is a nucleus that connects to all muscles does that mean we could get paralyzed from it "switching on" by mistake? Yes:
- Cataplexy

Cataplexy

- Name for paralysis induced by extreme emotion, happy or sad, in people who have "Narcolepsy"
- Narcolepsy is a pretty loose term that means anyone who can't stay awake during the day, i.e. someone who's sleep switches are very screwed up.
- They can also have "sleep paralysis", wake but can't move anything, screwed up switches again.
- They can "flip" at the wrong time, oops you're paralyzed, or become unlinked and not flip at the right time.

Sleep anatomy overlaps the anatomy of orgasm

Substantia Nigra



Nucleus reticularis pontis oralis

Reticular Formation keeps us conscious

Nucleus reticularis pontis caudalis

Could Cataplexy be the opposite of Orgasm ?

- Extreme emotion leading to paralysis? Switch goes "off"
- Extreme emotion, leading to orgasm, leading to involuntary body movements. Switch goes "on"
- Though this is an experience most people have had we expect it in a certain context
- What if the body movements happened without the accompanying sensory events?
- What would that look like?

What happens if I have something the doctors haven't written about?

- What if my body does things that haven't been named?
- If something has a name I can google it and learn about it, but what if it doesn't have a name?
- What if it isn't understood and isn't named but it has just happened to me?
- All of a sudden my body starts jerking I fall out of the chair and jerk on the floor, I can hear but not speak.
- They've told me it's not a seizure, it's a "pseudoseizure"

Pseudoseizures?

- Why would an otherwise healthy teenager have something like this happen to her?
- Does she have meningitis? A brain tumor? Drugs?
- What if there is no fever, the MRI is normal, the spinal fluid is normal, it happens several times with a headache following, and the EEG is normal?
- What if she was depressed in 9th grade and "cut herself"?

Is she crazy? Is she making it up?

- What if seizure medicines don't stop them?
- What does it mean if she can remember things people say to her during an attack?
- If she goes to school but has to sit on the floor in class so she won't fall out of the chair when she has one, does that mean she's afflicted or attention seeking?
- What happens when we tell her she's making it up? Why would she do that?

Healthy people can't be awake and asleep at the same time

- People with sick sleep switches can be awake and asleep at the same time or in states in between the two.
- Involuntary paralysis, involuntary movements, both jerking and dystonic
- Hallucinations?
- If this system is a self repairing neurologic circuit that is supposed to repair itself during sleep could it start to malfunction when someone doesn't sleep normally year after year?

What do I ask my patient?

- Inability to fall asleep or stay asleep?
- Inability to wake up or stay awake, feel tired despite sleeping?
- Trouble getting out of bed for school in the morning, trouble falling asleep at the usual time.
- Do you wake with pain in the morning? Childhood leg pain on awakening is a sleep disorder. Bedwetting is a sleep disorder.
- Do you talk, walk, snore kick, chew in sleep? History of sleep walking or night terrors.
- Do you take OTC sleep aides

What do I do to fix them?

- I think it's a cascade of events starting with a low vitamin D level but usually progressing to several other B vitamin deficiencies as well
- The D effect begins to fail after two years, the sleep begins to fail again and other things begin to show up.
- We do see patients daily who have B vitamin deficiencies that we have not been trained to look for, some affect the sleep.

Sleep related Neurologic Disorders

- Headache, vertigo, seizure, depression, memory loss are probably mostly related to inadequate REM sleep.
- We make permanent memories in sleep.
- We make the neurotransmitters that make the brain run normally in deep sleep.
- Serotonin reuptake inhibitors don't do much if there isn't any serotonin made because there is no REM.
- Tics, dystonia, tremor, cerebellar degeneration, perhaps some forms of Parkinson's all respond to improved sleep.

Sleep related disorders in children

- ADD, autism,
- Bedwetting
- Tics, seizures, tremor, headache, depression dystonia
- Obesity, acne, polycystic ovary disease, painful periods
- Leg and back pain on awakening
- Kids who sleep normally are not tired in the morning
- Teenagers with normal D/B levels do not have a hard time falling asleep at night
- Sleep is involuntary they're not "doing it wrong"

So what should we do instead?

- Learn more about sleep, teach our patients to protect their sleep.
- If they can't sleep don't blame them for their own disease
- Believe what they tell us about their sleep or lack of even if we don't understand why.
- Stop thinking about the back of the throat, start thinking about the brain and how we get paralyzed in sleep.
- Stop telling our patients they're crazy because we don't understand what's wrong, just admit we don't know.

Budding Professional Athlete

Budding Professional Athlete