

Resolving Restless Legs

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Resolving Restless Leg Syndrome

RLS seems related to or accompany the following underlying conditions:

1. End-stage renal disease and hemodialysis
2. Iron deficiency
3. Certain medications that may aggravate RLS symptoms, such as antinausea drugs (e.G. Prochlorperazine or metoclopramide), antipsychotic drugs (e.G., Haloperidol or phenothiazine derivatives), antidepressants that increase serotonin (e.G., Fluoxetine or sertraline), and some cold and allergy medications that contain older antihistamines (e.G., Diphenhydramine)
4. Excessive use of alcohol, nicotine, and caffeine
5. Pregnancy, especially in the last trimester; in most cases, symptoms usually disappear within 4 weeks after delivery
6. Neuropathy (nerve damage).

Resolving Restless Legs

What are the common denominators?

1. Inflammation
2. Iron deficiency (particularly ferritin)
3. Dopamine levels and dopamine receptors
4. Irritable bowel / SIBO issues
5. Common nutritional deficiencies
6. Loss of calcium homeostasis
7. Chronic stress (stress depletes dopamine levels)

Bowel Issues

- IBS was diagnosed in 28% of subjects with restless legs syndrome, compared to 4% of the controls.
- The breath test showed SIBO was present in 69% of the people with restless legs syndrome, compared to 28% of the controls.
- The conclusion: people with restless legs syndrome have a greater incidence of problems in the digestive system - than people without it.
- Rifaximin (anti-biotic) improved IRLS scores for all 20 patients compared with the placebo group, which had no significant improvement from baseline. [\(1\)](#)
- Antibiotic therapy may improve idiopathic restless legs syndrome: Prospective, open-label pilot study of rifaximin, a non-systemic antibiotic. http://www.gidoctor.net/client_files/file/LW_sleep_medicine_letter_to_editor.pdf

Iron levels and Dopamine

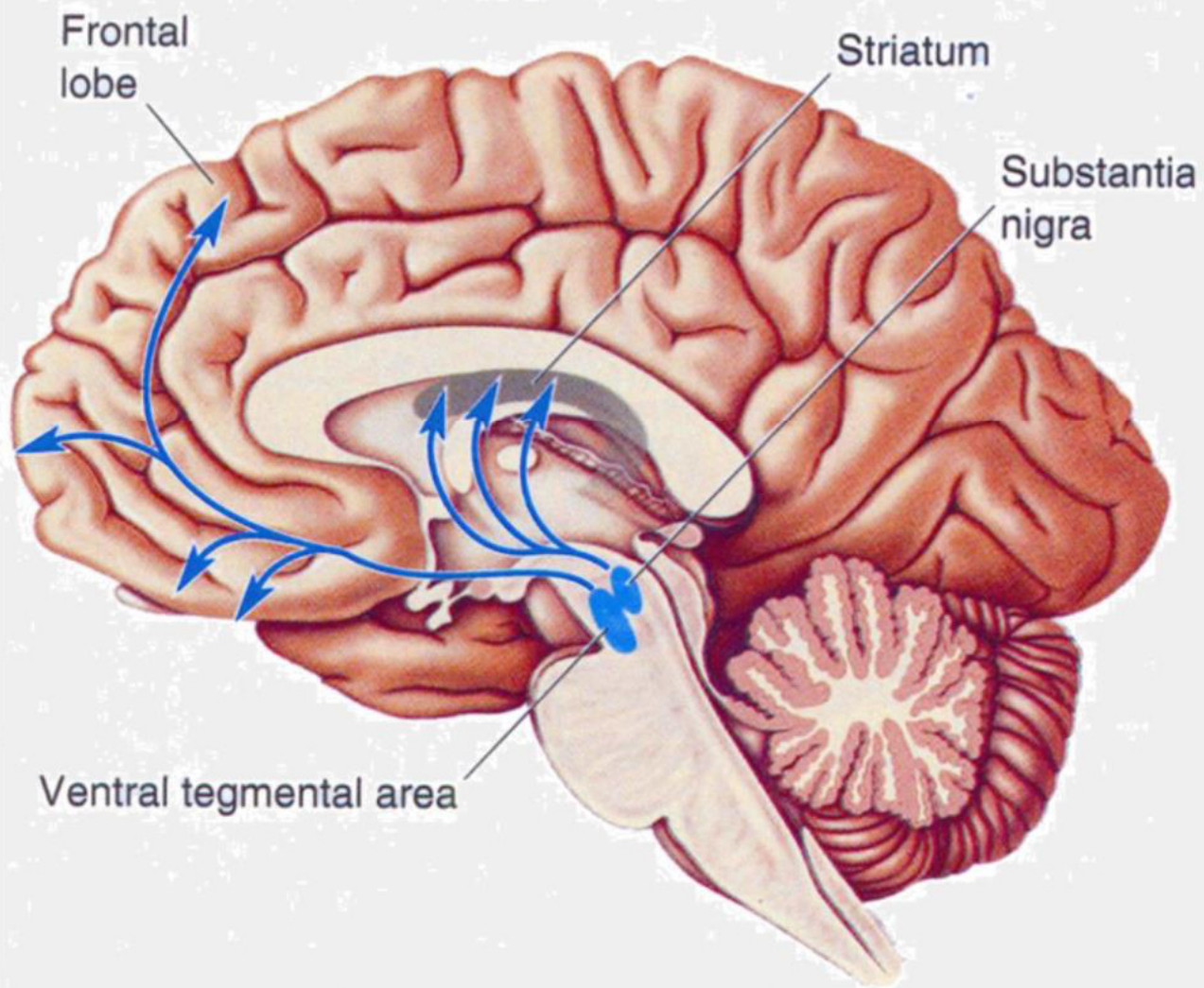
- Iron deficiency in the substantia nigra could impair dopaminergic receptors or transporters.
- At the present time, there is robust evidence that low iron levels are one of the causative factors of RLS or of increasing its severity.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882550/>

- *Scientists have also found that the root of many restless leg cases is the body's ability to transport dopamine.*
- *Based on autopsies of people claiming to have had RLS during their lifetime, researchers have found that lack of dopamine was not the problem, instead, it was the dopamine receptors that were not functioning properly.*

https://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/restless-legs-syndrome/what-is-rls/causes.html

Dopamine system



Thyroid Levels

Among the associated clinical features of RLS, as stated by the IRLSSG, is a serum ferritin level $<50 \mu\text{g/L}$.⁷ **Ferritin, an iron-binding protein** is, at low levels, one of the most sensitive **indicators of iron deficiency**. Iron is a cofactor of tyrosine hydroxylase, a limiting enzyme in the **synthesis of (dopamine) DA**. Local iron deficiency in the substantia nigra could impair dopaminergic receptors or transporters. At the present time, there is robust evidence that low iron levels are one of the causative factors of RLS or of increasing its severity.⁸⁻¹⁰ Diminished DA function has a role in RLS symptoms, as can be inferred from the fact that DA agonists are beneficial to RLS patients, whereas antagonists are detrimental, and **low iron levels are a putative cause of decreased DA function.**⁸

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882550/>

Thyroid Levels

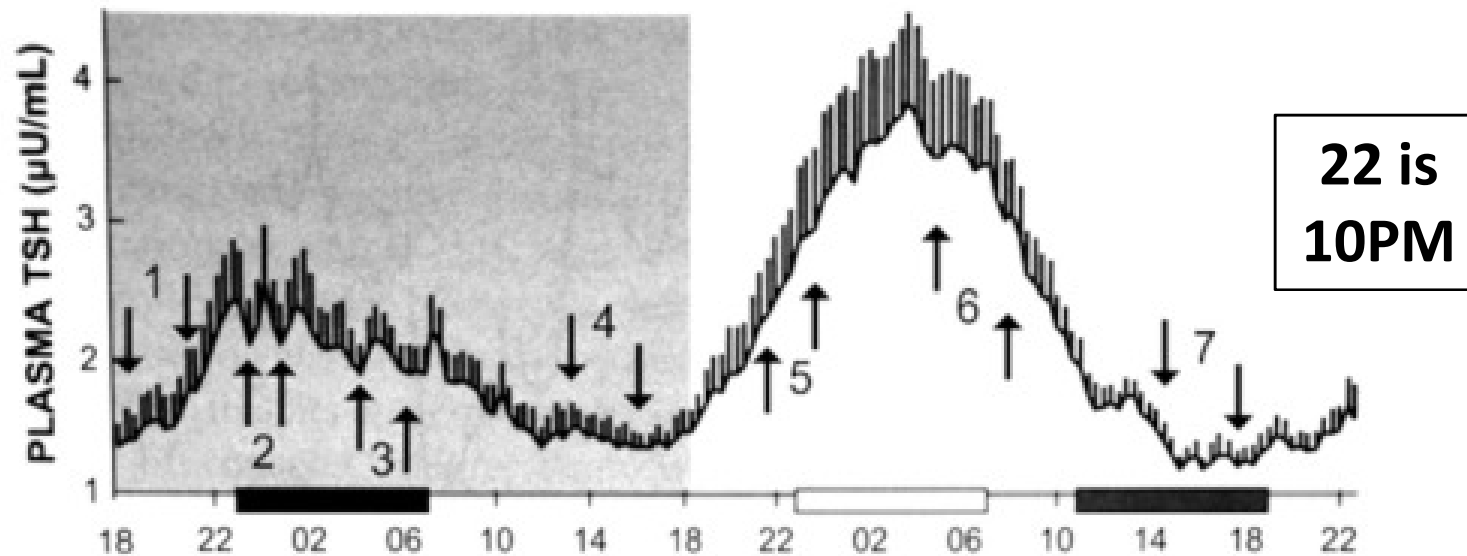
- Conditions associated with higher levels of thyroid hormones, such as pregnancy or hyperthyroidism, have a higher prevalence of Restless Legs Syndrome symptoms.
- Some of the effects of increased TH, such as hyperthyroidism, resemble some symptoms of RLS patients.[21](#), [22](#)
- Dopaminergic agonists (compounds that activate dopamine receptors) alleviate Restless Legs Syndrome symptoms.
- The daily profile of thyroid-stimulating-hormone (TSH) levels resembles the daily circadian intensity profile of symptoms of an RLS patient.
- Levels of TSH increase in the evening, as does the severity of RLS symptoms.
- Drugs that increase dopamine diminish TSH.
- As a result of low iron levels, dopamine levels decrease and thyroid hormones increase.
- Iron therapy improves Restless Legs Syndrome symptoms in iron deprived patients.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882550/>

Thyroid Levels

- One mechanism by which T4 and T3 is modulated by the dopamine system is through enhancement of cytochrome P450 (CYP450) enzymes.
- CYP450 isoforms are expressed in the liver (phase 1 detox) and other peripheral organs, and also in glial cells and neurons in the brain¹⁸
- The CYP450 enzymes are heme enzymes (all have iron) and the CYP450 enzyme superfamily is important for the biochemical degradation of T4 and T3. (*breakdown of T4 and T3*)
- Low iron levels diminish the quantity of CYP450 available to degrade T4 and T3. (*So low CYP450 means increased T4, T3*)
- Several drugs that alleviate the symptoms of RLS are inducers of CYP450 activity, which leads to diminishing T4 and T3.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882550/>



NOCTURNAL SLEEP



NOCTURNAL SLEEP DEPRIVATION



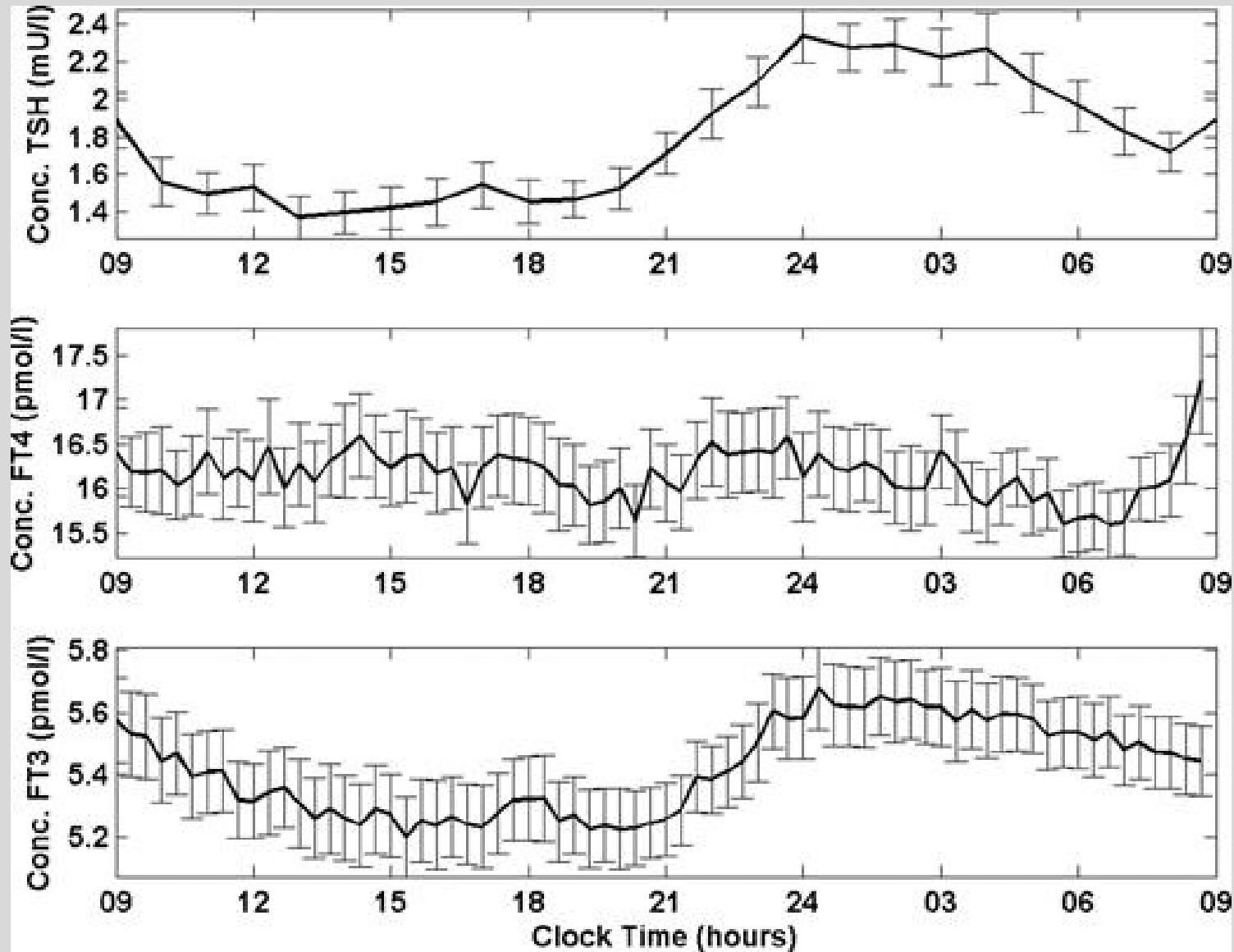
DAYTIME SLEEP



- 1- TSH evening steep increase: lowest propensity to sleep in the biological day. Worsening of RLS symptoms.
- 2- High biological night TSH: increased arousal necessity. Descending tips of TSH correspond to SWS. Goichot B, et al ⁽²⁵⁾
- 3- Low biological night TSH: .not so great arousal necessity
- 4- Lower biological day TSH: greatest biological day propensity to sleep.
- 5- Ascending TSH levels that permit sleep curtailment..
- 6- Descending TSH levels that allow recovery sleep.
- 7- Very low TSH levels: necessity of a recovery sleep. More deep NREM sleep.

Normal 24 Hour Rhythm of TSH, FT4, FT3

<https://academic.oup.com/jcem/article/93/6/2300/2598837>

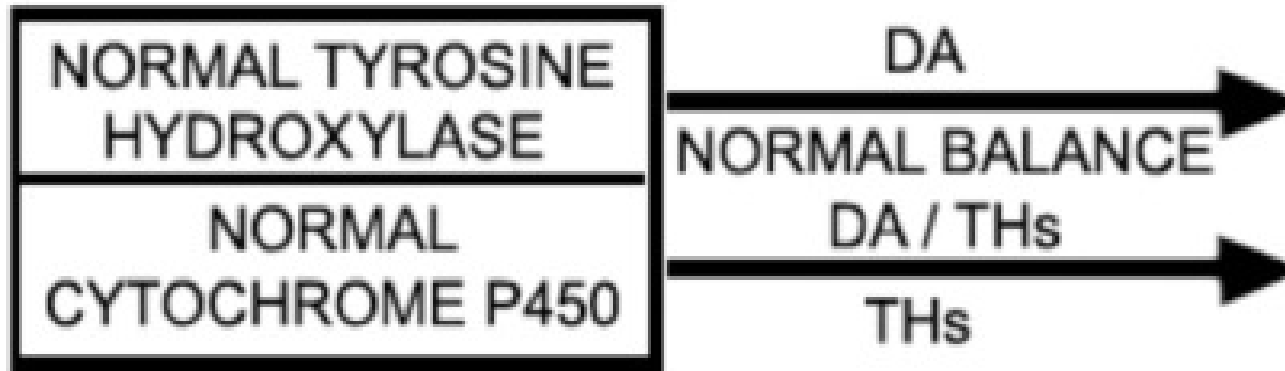


**21 is
9PM**

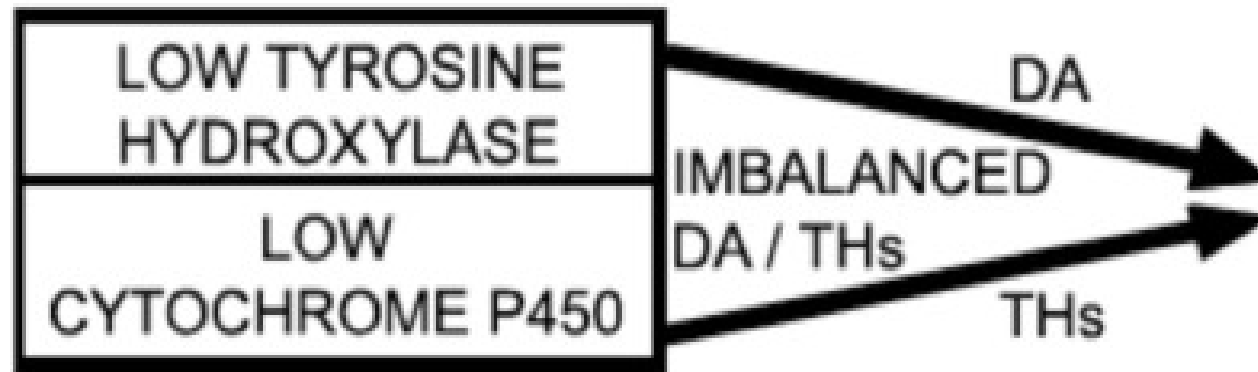
Thyroid and RLS

- RLS is noted for low iron *levels*. (*Perhaps inability to intestinally absorb iron?*)
- Hence there is insufficient iron to produce needed dopamine (*or perhaps dopamine receptors are dysfunctional due to toxins and nutritional deficiencies.*)
- TSH and T3 is naturally higher in the evening/night.
- Dopamine lowers TSH. Less dopamine means TSH is not diminished and would be even higher in evening/night.
- CYP450 enzymes lowers T4 and T3. CYP450 are heme (iron) enzymes. Insufficient iron means less CYP450, thus T4 and T3 would be even higher in evening/night.
- When the normal circadian rhythm of TSH, T3 are bio-rhythmically higher in evening/night and then TSH, T3, and T4 are excessively increased due to lowered dopamine and lowered CYP450 levels, the body has a hyperthyroid effect , has symptoms, and is less able to sleep.

NORMAL IRON LEVELS



LOW IRON LEVELS

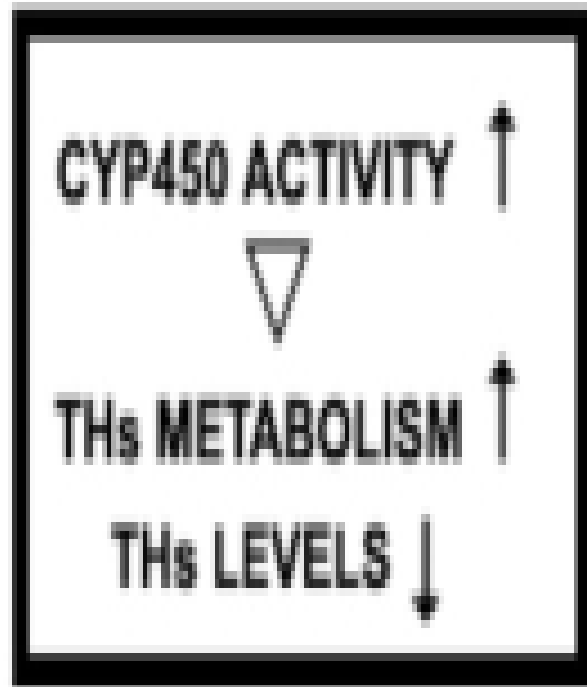


Low Iron = Low Dopamine = Increased TSH

Low Iron = Low CYP450 = Increased T4 and T3

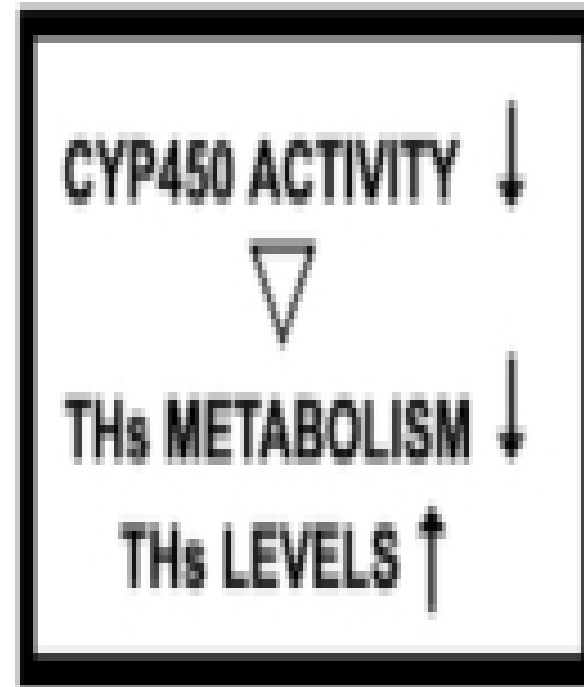
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882550/>

CYTOCHROME P450 INDUCERS



T4 and T3
↓

CYTOCHROME P450 INHIBITORS



↑
T4 and T3

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882550/>

Drugs that Effect Thyroid and RLS

- Some of the effects of increased TH, such as hyperthyroidism, resemble some symptoms of RLS patients.^{[21](#), [22](#)}
- Opioids, the first class of drugs used to treat RLS,^{[3](#), [5](#)} are also known to depress the TH axis.^{[36](#),[37](#)}
- Some drugs that are effective against RLS symptoms, such as carbamazepine, phenobarbital, valproate, and primidone are inducers of CYP450 enzyme activity.^{[38](#)}
- Selective serotonin reuptake inhibitors, neuroleptics, tricyclic antidepressants, and antihistamines are all CYP450 inhibitors,^{[39](#)} and they all worsen the symptoms of an RLS patient.^{[3](#),[5](#)}

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882550/>

Growing Pains

- “Growing pains” are common in childhood RLS,⁵¹ and some adult patients also complain of pain concomitant with other classical symptoms of RLS in the legs.^{3,5}
- A very important study by Ondo and colleagues (2000) demonstrated that the dopaminergic system in rats sends long projections from the midbrain into the spinal cord, which influences the gating of peripheral nociceptive input.⁵² With the profuse data demonstrating the tight interactions between TH and DA, it seems plausible that TH mediates these nociceptive inputs and that pain ensues when these inputs are not counterbalanced by DA.
- Growing pains occur mainly in the evening or night when TH levels are higher; they usually do not occur during the day when TH levels are lower.
- Rye and Freeman explain that the physiological effects of the DA system are best characterized as “neuromodulatory,” rather than eliciting excitatory or inhibitory postsynaptic potentials.⁵³
- From the considerations about RLS clinical and physiopathology issues described above, it is possible to infer that the DA system also has a hormonal modulatory effect on TH.

Thalamic (part of brain) glutamate/glutamine in restless legs syndrome

- RLS pathophysiology may involve 2 different neurotransmitter systems, dopamine and glutamate (Glu), each primarily related to different clinical features of RLS.
- The Glu and dopamine abnormalities may combine and interact to produce the full range of RLS symptoms, i.e., dopamine related more to sensory symptoms and PLMS, Glu related more to the RLS hyperarousal with sleep disruption.

The conclusion is that it is the combination of glutamatergic (sleep disturbance) and dopaminergic (sensory symptoms, PLMS) abnormalities that produce the full RLS symptomatology.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3716406/>

Glutamate and the Methylation pathway

- if there is impairment in the methylation pathway, then folate doesn't get utilized and it can break down into glutamate.
- Methylation is a biochemical process involving the transfer of an active methyl group between molecules. Methylation is required for cell division, DNA and RNA synthesis, early CNS development, gene expression, immune cell differentiation, post-transcriptional modification, **neurotransmitter synthesis and metabolism**, histamine clearance, detoxification, hormone clearance, cellular energy metabolism, phospholipid synthesis, and myelination of peripheral nerves.
- Methylation may be impaired due to nutritional deficiencies, toxins, genetic mutations, or Candida overgrowth.
- **The two most important nutrients in methylation pathways are B12 and folate.**

The Methylation cycle

- The methylation cycle is important because it takes the nutrients from our food (and supplements) to make the energy our bodies need to work properly. I often refer to it as the “B vitamin Cycle” because this is where the B vitamins (B1, B2, B3, B6, B9, B12) get used in our bodies and why B vitamins are so important for our health.
- Once through the methylation (B vitamin) cycle, our bodies use methyl-groups to make healthy cells and **neurotransmitters** (for mood), as well as for removing toxins (in the liver), fighting infections and protecting us from oxidative stress.
- Methylation is a metabolic process in the human body that helps **make and eliminate neurotransmitters** and this affects cognition and mood, it protects nerves and helps in detoxification and gene expression.

Glutamate

1. Glutamate has the ability to bind with six other receptors in the brain, like the NMDA receptor, which assists in **delivering calcium to the cell** and plays a vital role in memory function and synaptic plasticity.
2. **Calcium is used by glutamate** as the agent that actually inflicts the harm on the cell. So, if there is an excess of calcium in the body for any reason, it too will contribute to the GABA and glutamate imbalance.
3. **Loss of calcium homeostasis is a key mediator of glutamate-induced cell death. The neurotransmitter dopamine (DA) is known to modulate calcium signaling.**
4. Glutamate and calcium together cause ongoing firing of the neurons, which triggers the release of inflammatory mediators, which leads to more influx of calcium. It becomes a vicious cycle that results in neural inflammation and cell death.
5. Glutamate has been described as the gun, while calcium should be seen as the bullet, says Dr. Mark Neveu, a former president of the National Foundation of Alternative Medicine.

Glutamate Receptors

Glutamate receptors also pull in other excitatory substances into the cell beside glutamate, including all of the following:

1. Aspartate (can also be converted into glutamate)
2. Aspartame
3. Aspartic acid
4. Glutamic acid
5. Glutamine
6. Monosodium glutamate (MSG)
7. Cysteine
8. Homocysteine

Natural Sources of Free Glutamate

1. Foods matured, cured, or preserved, such as matured cheeses (Parmesan and Roquefort) and cured meats
2. Fish sauce
3. Soy sauce and soy protein
4. Mushrooms
5. Ripe tomatoes
6. Broccoli
7. Peas
8. Walnuts
9. Grape juice
10. Bone broths and meats cooked for long times (generally using moist cooking methods such as braising)
11. Malted barley used in breads and beer
12. Wheat gluten
13. Dairy casein

Free Glutamate

Free glutamate may be listed as any one of a number of the following ingredients:

Monosodium glutamate, monopotassium glutamate, yeast extract, anything “hydrolyzed” such as hydrolyzed protein, calcium caseinate, autolyzed yeast, textured protein, gelatin, soy protein (including isolate and concentrate), whey protein (including isolate and concentrate), carrageenan, bouillon and broth, stock, and “flavors” or “flavoring” (i.e. natural vanilla flavor), maltodextrin, citric acid, pectin, milk powder, soy sauce, anything “protein fortified,” corn starch, corn syrup and modified food starch.

Glutamate

Other foods or substances that contain excitotoxins and can damage nerves include:

Anything fermented, protein fortified, or ultra-pasteurized, or vitamin enriched, corn syrup, body builder formulas or protein formulas, caramel flavoring or coloring, flowing agents, dry milk, L-cysteine, egg substitutes, cornstarch and some brands of corn chips, citric acid if it is processed from corn, certain brands of cold cuts, hot dogs and sausages (even the ones in health food stores), many canned foods, pectin, pickles, any processed food, meats in mainstream grocery store are often injected with them, tofu or other fermented soy products, xanthan gum or other gums.

Glutamate

1. **Magnesium** will help regulate calcium levels and so can zinc. (Mag. Is also anti-inflammatory and can help muscles relax.)
2. Lithium, as well as iodine and boron, can also assist in lowering glutamate. (Excess iodine may also raise thyroid levels.)
3. Calcium intake may need to be reduced or limited if calcium is too high.
4. The toxins created by Candida, mold, and bacteria can stimulate surges of glutamate production.
5. Some people may have a genetic predisposition to have more glutamate receptors than others, and the more glutamate receptors you have, the more you will take in.

Glutamine for Gut Repair

- Glutamine is often recommended to heal the gut and can increase GABA, but it first increases glutamate.
- If you aren't converting your glutamate to GABA, then you end up with excess glutamate.
- Bone broth (esp. chicken) and whey protein also contain glutamate.
- This is why some with RLS see an increase of symptoms with bone broth and whey protein.

Vitamin D and K Required for Calcium Homeostasis

- The findings of this study support the hypothesis that RLS is more frequent and more severe in vitamin D deficiency.

<https://www.ncbi.nlm.nih.gov/pubmed/25904436>

- Vitamin D and its' metabolites are a crucial part of the endocrine system that controls whole body calcium homeostasis.

<https://www.ncbi.nlm.nih.gov/pubmed/28400273/>

- A possible explanation for the negative effects of high-dose (1000 mcg daily), long-term intake of calcium on cardiovascular health is that it renders the normal homeostatic control of calcium concentrations in the blood ineffective.6

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4566462/>

Vitamin D3

- The role of vitamin D in dopamine signaling is only beginning to be investigated, but some evidence indicates that vitamin D could play an important role by increasing levels of dopamine and its metabolites in the brain, as well as protecting dopamine-associated neurons from toxins. ([13](#))
- RLS has been associated with vitamin D deficiency in several studies, and disease severity has been inversely correlated with vitamin D levels. ([14](#), [15](#), [16](#)) One study has also found that vitamin D supplementation improved the severity of RLS symptoms. ([17](#))

<https://chriskresser.com/4-little-known-causes-of-restless-legs-syndrome/>

Iron

- If the cause is SIBO, increasing iron intake can often make matters worse by creating an environment that promotes pathogen growth.
- The very best food source of iron is liver preferably pork. (*not kosher or Levitical*)
- Hem iron is the most bio-available of the bound forms of iron, and that means flesh foods; lean red meat, lamb, buffalo, wild game, sockeye salmon, tuna, pork and chicken legs.
- The next best are molasses, sesame seeds, pumpkin seeds, pistachios, the herbs dandelion, coco, rice bran, spirulina and cold water kelp.
- Bovine ferritin or ferrous glycinate are non constipating.

Folic acid and B12 and RLS

- Recent studies indicate that people suffering with RLS have low ferritin iron storage protein levels within the brain. If the ferritin iron storage protein level is below 50 mcg/L, dopamine production decreases in the body.
- Folic acid and B12 are known to increase ferritin iron protein levels within the brain, thereby naturally aiding dopamine transport and a decrease in RLS symptoms.

Dietary sources of vitamin B12

Vitamin B12 Food	Serving size	B12 (mcg)
• Clams	3 ounces	84
• Liver	3 ounces	70.7
• Trout	3 ounces	5.4
• Salmon	3 ounces	4.9
• Tuna, canned	3 ounces	2.5
• Beef	3 ounces	1.5
• Nonfat plain Greek yogurt	6 ounces	1.3
• Low-fat milk	1 cup	1.2
• Ham	3 ounces	0.6
• Egg	1 large	0.6
• Chicken breast	3 ounces	0.3

Source: National Institutes of Health

Recommend: Sublingual Methylcobalamin with methyl-folate

Beneficial Bacteria

Four reasons beneficial bacteria are critical for
RLS symptoms

1. For the adequate absorption and assimilation of iron
2. The proper absorption of B vitamins
3. The production of Vitamin K
4. And the protection against pathogens and inflammation

What promotes or worsens RLS symptoms

1. Low iron, ferritin levels
2. Low CYP450
3. Hyperthyroid conditions
4. Low B12 and folate levels
5. Low Vitamin D3 levels (Needed for healthy calcium metabolism)
6. Low Vitamin K levels (Needed for healthy calcium metabolism where it reacts with glutamate and calcium)
7. SIBO issues (Low HCl, bowel inflammation, intestinal pathogens, vagus nerve, ileocecal valve issues)
8. Lack of beneficial gut bacteria
9. Toxins created by Candida, mold, and bacteria can stimulate surges of glutamate production
10. Excess calcium supplementation (imbalance magnesium and calcium homeostasis)
11. Magnesium deficiency (extremely helpful in lessening RLS symptoms)
12. MSG and Glutamate foods and cooked milk
13. Dehydration (bowels and nerves and brain need water)
14. Inflammatory foods such as hydrogenated oils
15. Elevated blood level of C-reactive protein (a marker of systemic inflammation - Gut reactions)
16. Excessive use of alcohol, nicotine, and caffeine (lowers B vitamins, increases cortisol, and nerve irritants)

What to do to resolve RLS?

1. Increase iron/ferritin levels with bovine ferritin or ferrous glycinate
2. Take methylcobalam (B12) and (MHTHR) folate levels – bedtime is better
3. Increase as needed Vitamin D3 levels (best to take with Vitamin K) (Needed for healthy calcium metabolism, because it reacts with glutamate and calcium)
4. Work on SIBO / IBS issues (herbal anti-biotics are especially important)
5. Take a quality high potency multi-vitamin mineral (B complex)
6. Increase HCl with meals (Betaine HCl or ACV or celery juice or herbal bitters)
7. Support beneficial gut bacteria when applicable with SIBO program
8. Take extra magnesium
9. Remove offending foods: MSG, glutamate foods, cooked milk, inflammatory foods such as hydrogenated oils, and GMO foods
10. Stay hydrated, get plenty of fiber, and keep the bowels regular
11. Avoid excessive use of alcohol, nicotine, caffeine, and calcium supplementation
12. Manage stress (get sleep when you can)
13. Exercise and stretch the low back out to relieve pressure on the nerves
14. Detox your gut and your brain

Next Week

Affordable Anti-aging

PDFs of the presentations are available at

**[https://www.lifetraininginstitute.org/
resource-links.html](https://www.lifetraininginstitute.org/resource-links.html)**