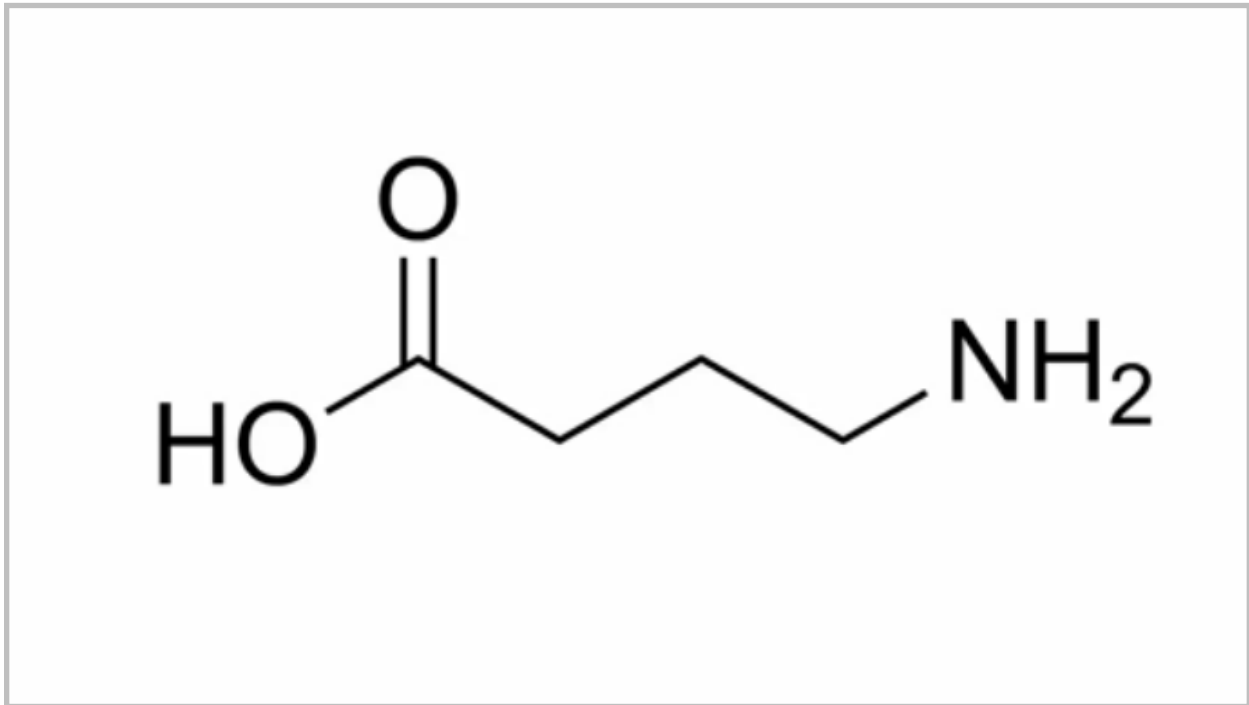


HPA-D 3-5 – Part 8

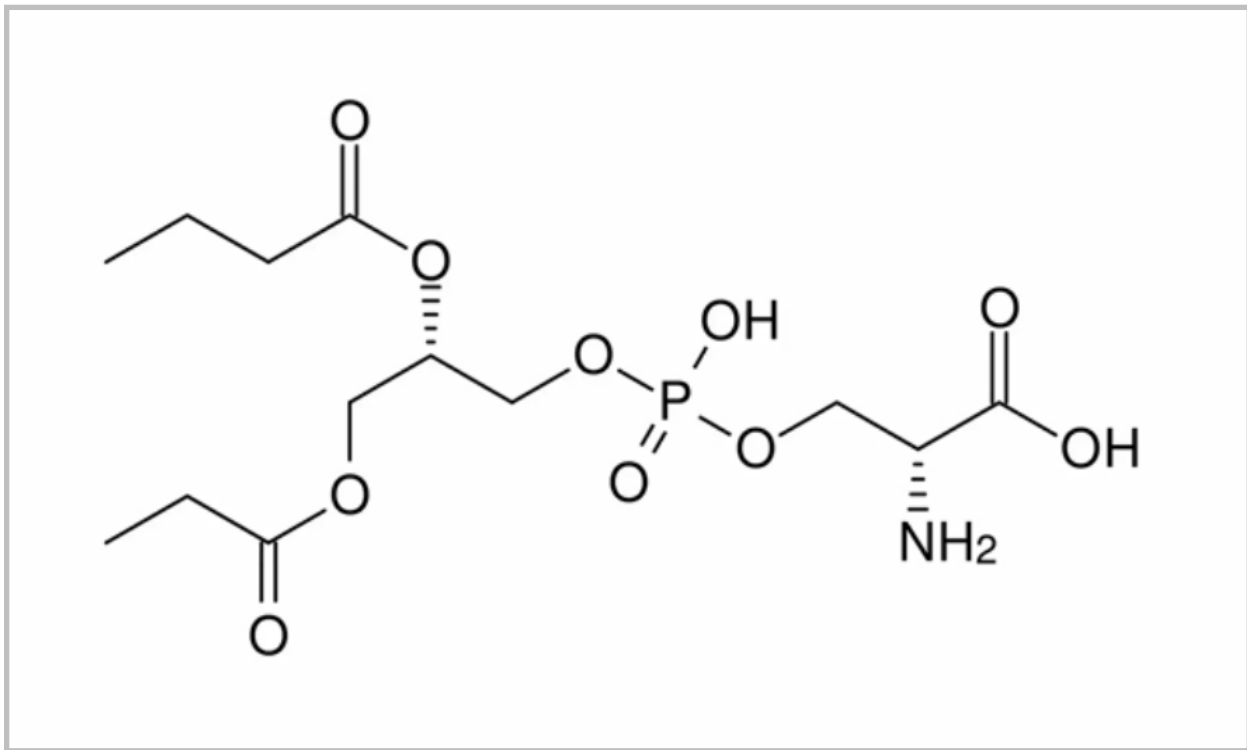
Next up is [gamma aminobutyric acid] (GABA). GABA is an amino acid [that] acts as a neurotransmitter in the central nervous system.



It's the major inhibitory neurotransmitter, so you can think of it as the off switch for the nervous system. Most supplemental forms of GABA don't cross the blood-brain barrier and thus won't be really effective because GABA is such a large molecule. But some forms do, and one of those is PharmaGABA and another is phenibut, or 4-amino-3-phenylbutyric acid, a phenylated version of GABA.

Previously, and you may remember us mentioning this in various posts, podcasts, and articles, we used Kavince, which is a blend of taurine and the 4-amino-3-phenylbutyric acid. We found it super effective in practice, but it has since been taken off the market after the [U.S. Food and Drug Administration] warned that phenibut cannot be used in dietary supplements, and that it may be the most impotent ingredient in the formula. So, unfortunately, since they removed that synthetic anxiolytic compound, it works by boosting the levels of inhibitory neurotransmitter GABA in the brain. Its frequent use can lead to addiction, and as a result, the product is no longer available with the phenibut in it. But we did find it to be very effective in practice. You still can purchase phenibut as a supplement on its own, but it really should be taken with caution and due diligence. It should be done to explain the potential addictive nature of the substance. In practice, we didn't have any issues with it [for] addictive purposes. But we would generally

recommend about 250 to 500 milligrams a day [maximum] and then usually about two to three times a week. So not taking it every day to reduce the risk of dependence.



Phosphatidylserine (PS) is a naturally occurring phospholipid. It's essential for the membranes of all cells, especially in the central nervous system. We make most of our own phosphatidylserine and absorb it well from diet, but supplementation has been shown to provide additional benefit in some cases. For example, one study in Italy showed that phosphatidylserine blunts [adrenocorticotrophic hormone] (ACTH) and cortisol response to physical and mental stressors. It may alter membrane fluidity with a neuronal signaling of the HPA axis and prevent heat shock protein membrane translocation as part of the cellular stress surveillance system. The dose used for the therapeutic effect of phosphatidylserine in most studies is quite high, ranging from 400 to 800 milligrams a day, though some have shown benefits at even 200 to 300 milligrams per day. Phosphatidylserine is one of the few supplements that has been shown to reduce cortisol levels, although GABA has been shown to do that in some studies, as well. Note that most soy-derived phosphatidylserine preparations will not trigger soy allergen issues. But there are now sunflower-derived phosphatidylserine products that are available, as well, for those who are concerned about soy either from the perspective of allergy or GMO. Integrative Therapeutics has a good brand of phosphatidylserine that is soy-free.

Taurine is another nutrient that supports sleep. It's the second most abundant amino acid in the central nervous system. There's not a lot of published data on taurine and sleep, but taurine has

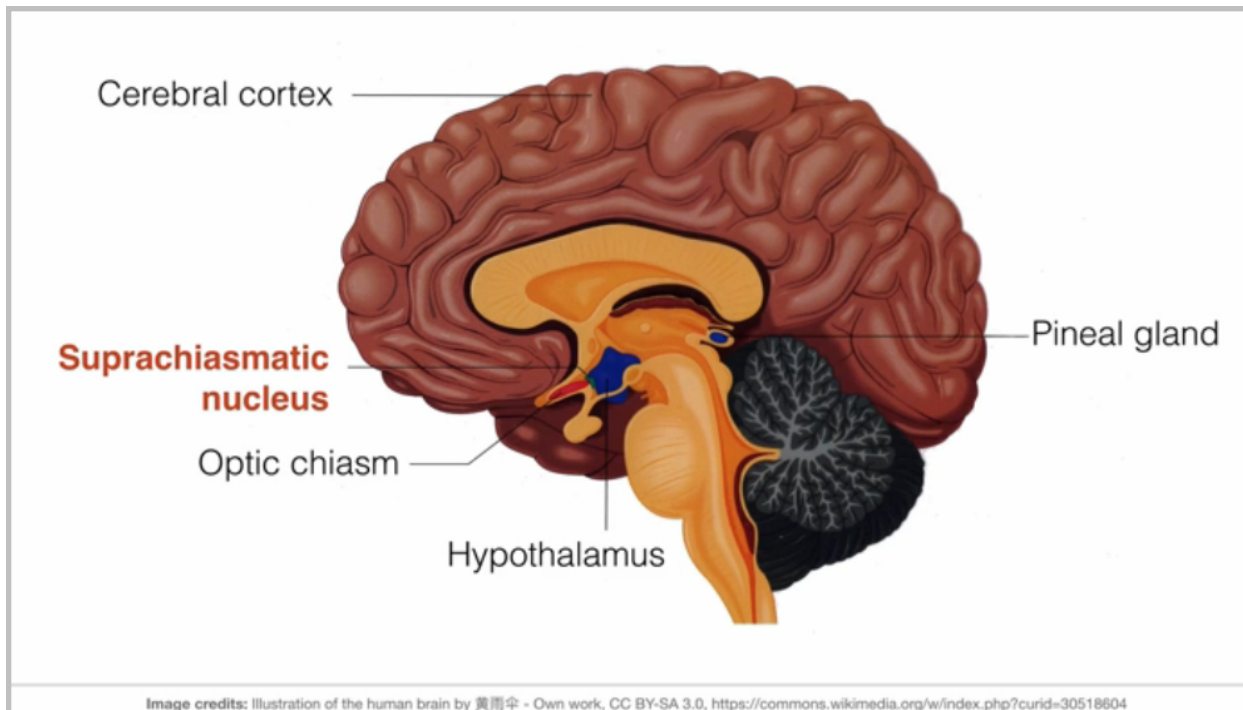
been reported to interact with neurotransmitter receptors involved in sleep regulation, including GABA-A, GABA-B, and glycine. Activation of GABA-A receptors counteracts the activation of NMDA receptors and the generation of nitric oxide. It has a wide margin of safety being well tolerated at 2 grams per day or even for most patients up to 12 grams per day as an adjunct therapy for liver disease. I don't typically prescribe this on its own, but if you do use it on its own and you want to get a higher dose, then I suggest a dose of 2 to 3 grams taken right before bedtime.

Five-hydroxytryptophan (5-HTP) is a naturally occurring substance derived from the seed pods of *Griffonia simplicifolia*, a Western Africa[n] medicinal plant. In humans, 5-HTP is the immediate nutrient precursor to the neurotransmitter serotonin, or 5-HT. 5-HTP increases serotonin levels in the brain, and supplementing with 5-HTP has shown to help reestablish healthy sleep patterns in people with chronic sleep disturbances. One of serotonin's metabolic pathways leads directly to melatonin. So, by increasing your levels of serotonin with 5-HTP, you're also increasing [the] levels of melatonin. A good dose of 5-HTP is typically 50 to 100 milligrams taken in the evening either at dinner time or bedtime. Definitely keep an eye on combination sleep supplements because they often contain some level of 5-HTP. So when making recommendations, always double-check to look at the ingredients to make sure that you are not getting too much 5-HTP from a combination of different supplements.

Melatonin is a hormone secreted by the pineal gland in the brain that helps regulate other hormones and maintains the body's circadian rhythm. Studies suggest that melatonin supplements can help people with disrupted circadian rhythms, such as people with jetlag, or those who work [the] night shift. They've also been shown to be helpful for those who have low melatonin levels in their labs like seniors and people with schizophrenia. Studies, however, suggest that it won't necessarily benefit people outside of these specific categories with sleep issues. So, in other words, if the person doesn't have low melatonin or [their] circadian rhythm isn't disrupted, it's not necessarily going to help with sleep. There are other causes to sleep disruption, and a dysregulated circadian rhythm and melatonin deficiency are only two of them. A wide range of doses have been used in melatonin studies. It's often taken by mouth 30 to 60 minutes prior to sleep time. Some evidence suggests that lower doses from 250 micrograms to 1 milligram may be more sedating than the higher doses, which are used for treating neuroinflammation and cancer. For sleep-onset insomnia, the sublingual form of melatonin is generally best because it's more rapidly absorbed and faster acting. But for sleep maintenance insomnia, where the patient has trouble staying asleep, an oral delayed-release form is better.

Melatonin is contraindicated in young children and pregnant and nursing women. It may reduce the effectiveness of antidepressant drugs and it may even worsen depression. Melatonin as a hormone has quite a few potential drug interactions, so we'll put a link with a list for some of these in the resources to make sure you take a [look at it].

L-theanine is a unique amino acid found in green tea and certain mushrooms. Half the population of the world drinks green tea daily, and L-theanine is second only to caffeine as the most consumed medicinal substance on Earth. The dose found in a cup of green tea is relatively small, so when taking higher doses as a supplement, it can have calming and focusing effects. It typically does not cause sedating effects during the day but can improve sleep naturally at night. Because theanine is metabolized by the same pathways as other amino acids in the body, there does appear to be little risk of tolerance or dependence.



Recent studies have shown a relationship between the cholinergic system and the suprachiasmatic nucleus (SCN). For example, the SCN has local cholinergic neurons. Acetylcholine has an excitatory effect on the SCN and resets the circadian rhythm. The theory is that cholinergic neural transmission in the SCN provides the brain with a mechanism to support the formation of time memory via something called time stamping. Since time stamping is a cholinergically mediated function of their circadian system, the early disruption of the cholinergic and circadian systems as seen in Alzheimer's disease may contribute to the cognitive disruption of temporal organization of memory and behavior in these patients. This means that nutrients that support the cholinergic system may help to reset their circadian clock and can be useful when the diurnal cortisol rhythm is disrupted.

Nutrients that support cholinergic system

Nutrient	Dosage
Alpha-GPC	200–300 mg/d
N-acetyl L-carnitine	50–100 mg/d
Huperzine A	150–300 mcg/d
Pantothenic acid	High dose, up to 1 gram/d

I've listed some of the nutrients that support the cholinergic system and acetylcholine synthesis on this slide. Pantothenic acid is used in the synthesis of coenzyme-A; it transports carbon atoms, which are important for the synthesis of acetylcholine. Alpha-GPC is a phospholipid metabolite used for the synthesis of acetylcholine. L-huperzine is an alkaloid that has a potent and special acetylcholinesterase-inhibiting effect, which results in decreased breakdown and increased levels of acetylcholine in the brain. Acetyl-L-carnitine has a structural similarity to acetylcholine and is thought to mimic its activity in the brain. It's best to use a formula combining all these typically to minimize the number of supplements a patient is taking. One formula I like that contains these four nutrients is Acetyl-CH from Apex Energetics, and the recommended dose is typically one capsule three times a day.

Summary of nutrients for HPA-D

Category	Dosage/Comments
Basic HPA axis support	Vitamin C, B vitamins, potassium, sodium, calcium, zinc, magnesium; take in multivitamin (without calcium), or individually
Glycemic control	Chromium, zinc, manganese, vanadium, gymnema, bacopa, etc. Metabolic Synergy & GlucoSupreme from DFH good options (no need for multi if you use Metabolic Synergy)
Inflammatory signaling	Curcumin, boswellia, skullcap, EPA/DHA
Circadian disruption	Botanicals (valerian, passionflower, jujube, hops), GABA, PS, taurine, 5-HTP, melatonin, L-theanine, pantothenic acid, alpha-GPC, huperzine A, N-acetyl L-carnitine

Here's a quick summary of the nutrients and botanicals for HPA dysfunction. For basic HPA axis support, we have vitamin C, B vitamins, potassium, sodium, calcium, zinc, magnesium, and you can take this in a multivitamin without calcium or individually, really the preference for you and the patient. For glycemic control, we have chromium, zinc, manganese, vanadium, jenama, and bukoba. Metabolic Synergy and GlucoSupreme from Designs for Health are really good options of combination products. And if you see this, you don't really need a multivitamin because it has a lot of the things that a multivitamin would have in it. So it's a nice substitute if you do have a patient taking a multivitamin, but you're also looking for herbs and nutrients to help control HPA axis or blood sugar regulation. For inflammatory signaling, consider curcumin, boswellia, skullcap, [eicosapentaenoic acid] (EPA), and [docosahexaenoic acid] (DHA). For circadian disruption, consider [a] botanical such as valerian, passionflower, jujuba, hops, GABA, phosphatidylserine, taurine, 5-HTP, melatonin, L-theanine, pantothenic acid, alpha-GPC, huperzine-A, and acetyl-L-carnitine. We've gone over [all of these] throughout the presentation, but here's just a nice little summary for you.