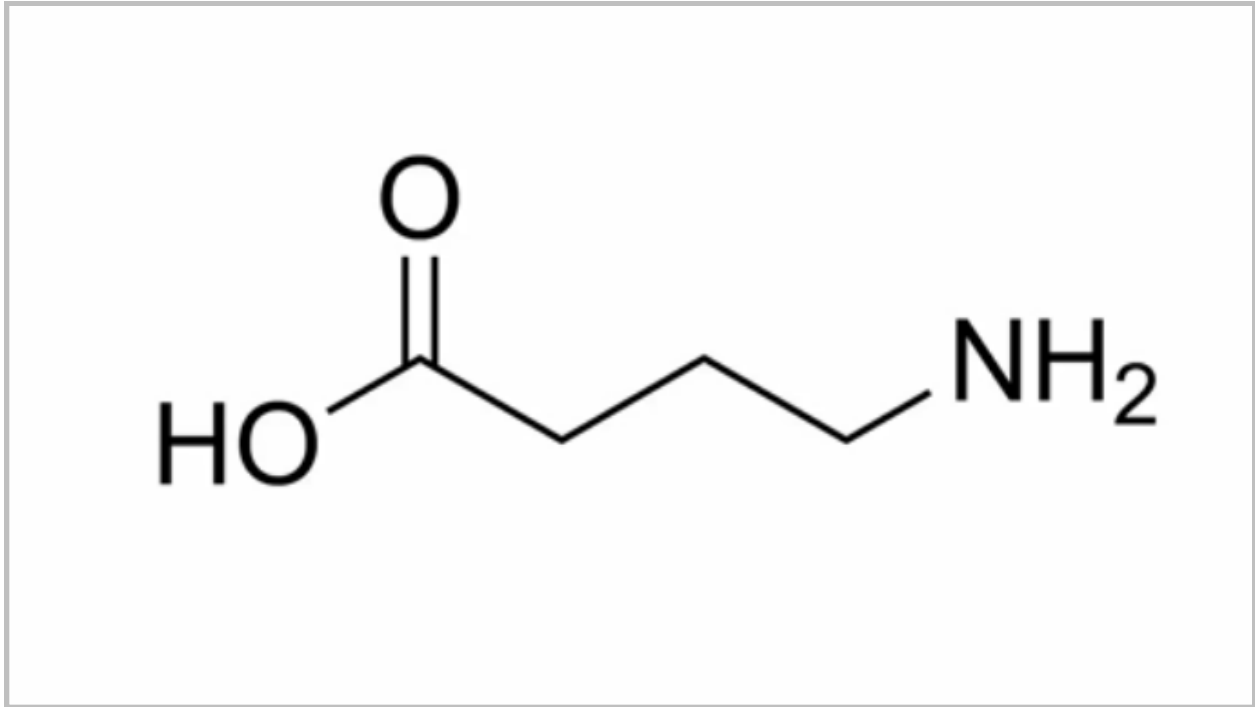


HPA-D 3-5 – Part 8

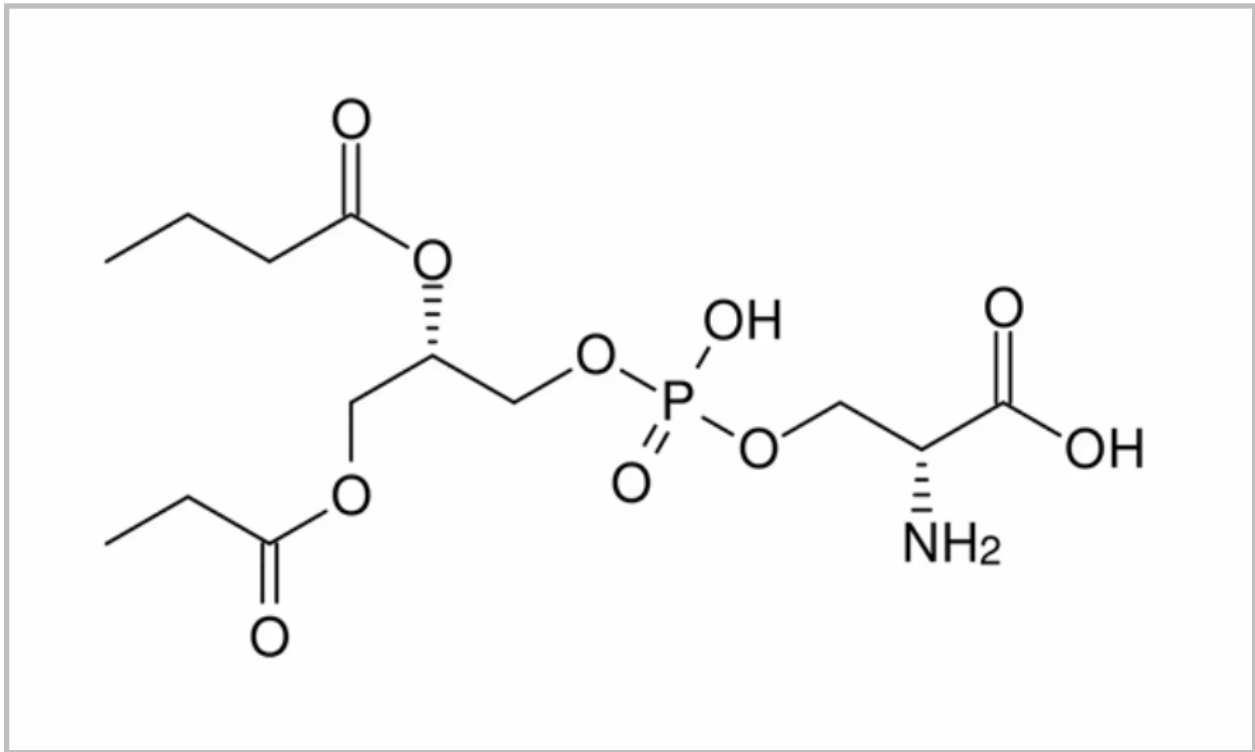
Next is GABA. This is an amino acid that acts as a neurotransmitter in the central nervous system.



It is the major inhibitory neurotransmitter. You can kind of 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 effective because GABA is such a large molecule, but some forms do, and one of those is pharmaGABA, and another is 4-amino 3-phenylbutyric acid. I use Kavince, which is a blend of taurine and 4-amino 3-phenylbutyric acid, in my practice, and it's extremely effective. Generally, one to two capsules before bed is a good dose for people who have difficulty staying asleep. They might still wake up a little in the night, but they'll have a much easier time falling back asleep, and they'll feel more rested when they wake up. Some of my patients really feel like Kavince is a complete lifesaver. For people who have trouble falling asleep, they can take Kavince an hour or two before when they'd like to go to bed, and that can help with sleep onset.

If you search a little online, you'll see some concerns about dependence for Kavince, and I think that is possible with higher doses that are used for anxiety, such as two capsules three times a day, but I personally have not seen it when Kavince is used at lower doses such as one to three capsules before bed in probably hundreds of patients now at our clinic. I've also seen patients who have taken it for up to two years or more and then have been able to stop cold turkey without any adverse effects. If the patient is concerned, you can pulse it, so they could take it four or five days

on and two to three days off, or maybe two weeks on and a week off. Like I said, that is rarely necessary, but if some patients are concerned, you can offer that as an alternative.



Phosphatidylserine, or PS, is a naturally occurring phospholipid. It is essential for the membranes of all cells, especially in the central nervous system. We make most of our own PS 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 PS blunts ACTH and cortisol response to physical and mental stressors. It may alter membrane fluidity within neuronal signaling of the HPA axis and prevent heat shock protein membrane translocation as part of a cellular stress surveillance system.

The dose used for therapeutic effect of PS in most studies is quite high, ranging from 400 to 800 mg a day, though some have shown benefits at 200 to 300 mg per day. PS 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 PS preparations will not trigger soy allergen issues, but there are now sunflower-derived PS 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 is the second-most abundant amino acid in the central nervous system. There is not a lot of published data on taurine in 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

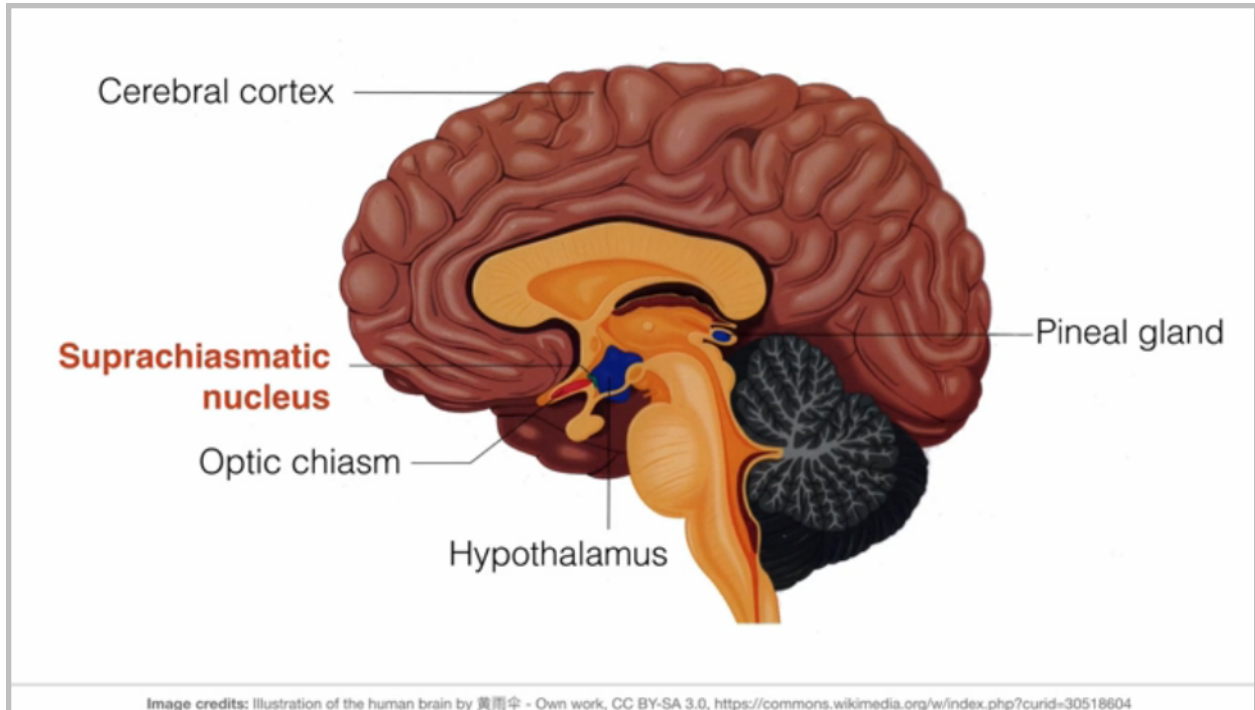
2 g per day or even, for most patients, up to 12 g per day as an adjunct therapy for liver disease. I don't typically prescribe it on its own, as it is in Kavinace, which I use regularly, but if you do use it on its own, and you want to get a higher dose, then I suggest a dose of 2 to 3 g taken before bedtime.

Five-hydroxytryptophan, or 5-HTP, is a naturally occurring substance derived from the seed pods of *Griffonia simplicifolia*, a West African medicinal plant. In humans, 5-HTP is the immediate nutrient precursor to the neurotransmitter serotonin, 5-HT. 5-HTP increases serotonin levels in the brain, and supplementing with 5-HTP has been 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 your levels of melatonin. A good dose for 5-HTP is 50 to 100 mg taken in the evening either at dinnertime or before bed.

Melatonin is the 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 jet lag or those who work the night shift, and those with low melatonin levels, such as some seniors and people with schizophrenia, to sleep better. It won't necessarily benefit people outside of these categories with sleep issues, however. So, in other words, if the person doesn't have low melatonin or her circadian rhythm isn't disrupted, it's not necessarily going to help with sleep. There are many causes of sleep disruption, and a dysregulated circadian rhythm and melatonin deficiency are only two of them.

A wide range of doses has been used in melatonin studies. It is often taken by mouth 30 to 60 minutes prior to sleep time. Some evidence actually suggests that lower doses from 250 mcg to 1 mg may be more sedating than higher doses, which are used for treating neuroinflammation and cancer. For sleep-onset insomnia, the sublingual form of melatonin is generally best because it is more rapidly absorb-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 worsen depression. Melatonin as a hormone actually has quite a few potential drug interactions, so we'll put a link with a list of some of these in the resources.

L-theanine is a unique amino acid found only in green tea and certain mushrooms. Half the population of the world drinks green tea daily. 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. When taken in higher doses as a supplement, it can have a calming and focusing effect. It does not cause sedation during the day, but it does improve natural sleep at night. Because theanine is metabolized by the same pathways as other amino acids in the body, there appears to be little risk of tolerance and dependence, so it can be very useful in HPA axis dysregulation.



Recent studies have shown a relationship between the cholinergic system and the suprachiasmatic nucleus. For example, the SCN, suprachiasmatic nucleus, has local cholinergic neurons. Acetylcholine has an excitatory effect on the SCN and resets the circadian rhythm. The theory is that cholinergic neurotransmission 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 the 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 the 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 synthesis of acetylcholine. L-huperzine A is an alkaloid that has a potent and specific acetylcholinesterase-inhibiting effect, which results in decreased breakdown and increased levels of acetylcholine in the brain. N-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 of these typically, just 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 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 is a summary of nutrients and botanicals for HPA-D. 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. For glycemic control, we have chromium, zinc, manganese, vanadium, gymnema, and bacopa. Metabolic Synergy and GlucoSupreme from Designs for Health are good options, and if you use this, you don't need a multivitamin because it has a lot of the things that a multivitamin would have in it. For inflammatory signaling, consider curcumin, boswellia, skullcap, EPA, and DHA. For circadian disruption, consider botanicals such as valerian, passionflower, jujube, hops, GABA, phosphatidylserine, or PS, taurine, 5-HTP, melatonin, L-theanine, pantothenic acid, alpha-GPC, huperzine A, and N-acetyl L-carnitine.