Serotonin and Headache: Using L-Tryptophan, 5-HTTP, and Other Methods to Increase Brain Serotonin Levels
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Key Points
1. Serotonin is a critical neuro-signaling chemical; a deficiency may result in chronic pains, sleep disturbances, anxiety, depression and a propensity to overeat.
2. Low serotonin levels are found in migraines and disorders they suffer with increased frequency including depression, irritable bowel syndrome, as well as, other chronic pain syndromes.
3. Serotonin can be increased naturally through behavioral health methods and dietary supplementation with pharmaceutical grade L-tryptophan or 5-HTTP; pros and cons exist for each.
4. The activity of serotonin can be altered with SSRIs, SNRIs, TCAs and MAOIs drug classes.

Serotonin and the Brain
Serotonin is a critical chemical neurotransmitter in your brain, gut and other nerve tissues. A neurotransmitter is a substance released by one nerve cell that allows communication with the cell next to it. Serotonin helps regulate pain, sleep, mood and appetite; a deficiency may result in chronic pains, sleep disturbances, anxiety, depression, and a propensity to overeat. Optimum serotonin may promote confidence, relaxation and feelings of personal security. A connection has been found between serotonin and headache. Migraine and in particular, chronic headache sufferers, tend to have low levels of serotonin, and their serotonin level goes even lower during a headache. This low basal or baseline serotonin level appears to make it easier for headaches to be triggered. In theory, increasing serotonin levels should help decrease the number of headaches, improve sleep and mood. Low serotonin levels have been discovered in other chronic diseases such as fibromyalgia, irritable bowel syndrome, premenstrual dysphoric disorder and depression to name a few. Narcotic pain medications lower serotonin levels, which may remain low chronically.

Methods to Increase Serotonin
Serotonin (or 5-hydroxytryptamine) levels can be increased in a number of ways – naturally by behavioral health methods, by dietary supplements or with medications. Some of these methods may be more effective than others, but most are easy to try and well-tolerated. Behavioral management methods that you can incorporate into your daily routine to increase serotonin levels include: exercise, a diet high in tryptophan (an extensive list can be found on Wikipedia: search tryptophan), brief exposure to bright light daily, positive thinking and avoidance of narcotics.

Commercially available dietary supplements can increase serotonin "naturally". Some that have shown promise include L-tryptophan, 5-hydroxytryptophan (5-HTTP), and vitamin B6. We will further discuss L-tryptophan and 5-HTTP. Prior to taking any supplement, you should first discuss it with your health care provider. Also, note that the Food and Drug Administration (FDA) oversight of manufacturing and quality control of over-the-counter dietary supplements is not as stringent as that required for prescription medications, but rule changes are in place for June 2010.

L-Tryptophan
L-tryptophan is an essential amino acid. Amino acids are critical to life as they are the building blocks of the body’s proteins. Essential amino acids must be eaten or supplemented as the body cannot make them. Tryptophan is the least plentiful in the diet of all the amino acids. A typical diet provides only 1,000 to 1,500 mg/day of tryptophan. L-tryptophan is the building block for serotonin and melatonin, so adequate body supplies are critical for optimal levels of both. L-tryptophan crosses the blood-brain barrier, which is necessary for serotonin to be made in the brain and spinal cord (i.e. central nervous system or "CNS"). While the amount of tryptophan in a typical diet meets basic needs, it often fails to provide optimal brain serotonin levels. The production of serotonin can vary, within the same person, and from day to day, because L-tryptophan competes with other amino acids to be transported into the CNS. The transport of L-tryptophan into the CNS can actually be inhibited by these other amino acids that are basically playing "musical chairs" waiting to be transported into the nerves. Because of this competition and enzymes that break down this amino acid, dietary tryptophan contributes very little to the brain and supplementation is typically required. Consuming L-tryptophan with a low-protein, high carbohydrate diet increases availability of this essential amino acid to the CNS. Production in the body of L-tryptophan can be decreased by stress and deficiency in vitamin B6.

Typical side effects are minimal with tolerance excellent for 500-3000mg per day. While helping sleep, morning hangover is not associated with L-tryptophan as it is associated with many other sleep aids. The FDA took L-tryptophan off the market in the United States about 20 years ago after several severe reactions were reported traced to a single Japanese manufacturer. Bacterial fermentation is required to manufacture L-tryptophan, and a contaminated batch caused an autoimmune illness called eosinophilia-myalgia syndrome, or EMS. EMS due to contaminated L-tryptophan was responsible for 38 deaths and 1500 illnesses. Though there have been no reported cases of EMS in the last several years, it is still important to be aware of the signs and symptoms. EMS is manifest by severe muscle pain, weakness, numbness, burning, tingling pain, twitching muscles, tremors, irregular heartbeat, and swelling.

An independent scientific committee has concluded that pure pharmaceutical grade tryptophan currently available is safe with no
association to EMS. Pharmaceutical grade L-tryptophan is available in the larger health food stores and over the internet without prescription, most commonly in 500mg and 1 gram strengths. A prescription form known as Tryptan™ comes in multiple dose strengths.

5-HTP
5-HTP is a metabolite (breakdown product) of tryptophan and a nonessential amino acid that contributes to increased production of serotonin, as well as, melatonin, dopamine, noradrenaline, and Beta-endorphins. These chemicals also play a role in sleep, mood, and pain regulation. 5-HTP (5-hydroxytryptophan) is directly converted to serotonin (5-hydroxytryptamine) in nerve cells and the liver. Due to this liver activity, 5-HTP from the gut is usually converted to serotonin before it can reach the brain. While blood levels of serotonin are thereby significantly increased, brain levels of serotonin are only slightly increased as blood serotonin has trouble entering the brain. In Europe, 5-HTP is often prescribed with a Parkinson drug, carbidopa, which prevents the conversion of 5-HTP into serotonin until it reaches the brain. In this setting, adequate 5-HTP crosses the blood-brain barrier increasing serotonin in the brain and CNS. Without this approach, due to the significant increased blood serotonin levels from liver production, several publications have raised concern of a significant risk of heart valve disease from serotonin's direct effect on the heart.

The supplement 5-HTP is made from a natural plant source (Griffonia simplicifolia) making its production potentially safer than that of L-tryptophan. Unlike L-tryptophan, the brain’s uptake of 5-HTP is not effected by other amino acids, which means that it is not competing with them for transport into the CNS.

Potential side effects of 5-HTP include nausea, gas (belching, burping and/or bloating and flatulence), and sometimes loose bowel movements or diarrhea. This is due to the ready conversion of 5-HTP to serotonin in the nerves of the intestines. (L-tryptophan is not converted to serotonin or 5-HTP in the gut and lacks these side effects.) However, side effects to 5-HTP are usually mild to moderate, often go away or at least significantly decrease after a few weeks and can be minimized by taking 5-HTP with meals. Theoretically 5-HTP supplementation, could cause EMS, as occurred previously before the availability of pharmaceutical grade L-tryptophan, but there are no published reports of EMS due to 5-HTP. In fact, there have not been any cases of EMS reported since 1998.

Medications
Serotonin can be increased by certain medications such as prescription antidepressants from the drug categories tricyclic (TCA), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors (SNRI). The SSRI’s and SNRI’s are the newest and generally most effective and well tolerated antidepressant medications available.

The SSRI’s work by increasing the level of serotonin available in the gap or junction between nerves. This happens by preventing its return to the nerve. Thus longer signaling time between nerves occurs in the CNS allowing nerve actions to continue more efficiently. SNRI’s work by increasing the content of both serotonin and norepinephrine in the nerve junctions by preventing their return to the nerve. While serotonin is increased in the nerve junction by all of these medications none really increase the total amount of serotonin in the nervous system. The biggest drawbacks to these medications are the potential side effects, including sexual dysfunction, high blood pressure, nausea, dizziness, insomnia and serotonin syndrome.

Serotonin Syndrome (SS)
Any of the above discussed products may be associated with the theoretical possibility of a rare but potentially severe, even life-threatening reaction known as ‘serotonin syndrome’. SS is essentially having too much serotonin. Life-threatening cases are mainly associated with MAOIs. There are no documented cases of SS occurring with 5-HTP supplementation. Although SS has been reported with the combination of tryptophan and an MAOI drug, the incidence of this disorder is very low. Signs and symptoms of Serotonin Syndrome are: agitation or restlessness, confusion, rapid heart rate, twitching muscles, heavy sweating, chills, diarrhea and headache. More severe symptoms included high fever, seizures, irregular heart rate and loss of consciousness. Most of the reported cases have occurred in people taking high doses of multiple medications that can elevate serotonin levels. See achenet.org for two detailed articles on SS. These can be found under ACHE News-Hot Topics and Information for Patients-Articles.

Evidence
Very few controlled research trials have compared the effectiveness of increasing serotonin by 5-HTP, L-tryptophan and antidepressants. Serotonin levels are as effectively raised by 5-HTP and L-tryptophan as TCAs and SSRIs in published trials. However, 5-HTP had the least side effects, and was significantly better tolerated than both the L-tryptophan and the antidepressant medications. That said, there have not been sufficient studies done comparing the “natural” versus “chemical” method of increasing serotonin to state absolutely that the supplements are as effective. No long term safety studies have been performed comparing these approaches. Also, there have not been any comparison studies of 5-HTP or L-tryptophan to the SNRIs.

Cautions
The use of 5-HTP and/or L-tryptophan should be approached with caution, particularly if you suffer from: cardiovascular disease, Parkinsons disease, liver problems, HIV or autoimmune diseases. Further, you should not use, unless under medical supervision, if you take any of the following medications: MAOIs, SSRIs, SNRIs, and tricyclic anti-depressant medications; barbiturates, tranquilizers, anti-histamine and OTC cold medications. They should not be used during pregnancy. It is recommended that before you begin using these and any other supplements that you discuss them with your health care provider.

Summary
Serotonin is an essential chemical nerve transmitter that helps to regulate many functions in the brain such as mood, pain, appetite and sleep. By increasing serotonin in the brain, people who suffer from frequent migraines, chronic headaches, depression, poor sleep and other pain conditions could possibly see a significant benefit. Using dietary means, 5-HTP or pharmaceutical grade L-tryptophan is relatively low cost, and potential side effects are typically mild if they occur at all. A reasonably practical program suggested to reduce deficiency of serotonin combines moderate amounts of tryptophan (500mg to 1500mg), 5HTP (33mg to 100mg) and melatonin (0.5mg to 1mg) taken at bedtime. (Other dosing regimens may be suggested by your health care provider) It may take up to 4 to 8 weeks of daily use before people notice significant changes, so one should stick with it if they do decide to try it. Certainly it is reasonable to discuss with your physician ways to naturally increase serotonin.

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