Studies which investigate the use of 5-HTP in the treatment of depression are very encouraging. 5-HTP appears to have equal efficacy to antidepressant medication, but without the drug risks and side effects.

Bioavailability and Conversion of 5-HTP to Serotonin

If 5-HTP is to be effective, it must, when given orally, cross the intestinal lining and make it into the bloodstream. Next 5-HTP must move from the blood into target tissues, such as the brain, and be converted into serotonin, the active neurotransmitter. Finally, the oral dose should correlate to the levels of serotonin in the nervous system.

The oral dosing of 5-HTP has been found to have a linear correlation to plasma levels. 5-HTP has been found in rat studies to be taken up by the brain from the blood and readily decarboxylated into serotonin. The ability of retinal tissue to convert 5-HTP into serotonin was found to be dose-dependent.

Depression

Many antidepressant drugs are assumed to bring about a mood-elevating effect by increasing the availability of serotonin in certain brain synapses (Figure 2). Unfortunately, these drugs can produce many unpleasant and dangerous side effects. Since 5-HTP cannot be patented as a pharmaceutical substance, drug companies have little profit incentive to market this natural substance. Tryptophan continues to be restricted by the FDA, and therefore researchers have been forced to look for alternatives by clinically investigating 5-HTP in comparison to antidepressant drugs. Studies which investigate the use of 5-HTP in the treatment of depression are very encouraging. 5-HTP appears to have equal efficacy to antidepressant medication, but without the drug risks and side effects. Similar studies with depressed children demonstrated equal benefits. Other studies have shown 5-HTP to have equal efficacy to antidepressant medication, especially in those who exhibited an anxious, agitated, or irritable mood. Even double-blind studies confirm the antidepressant effects of 5-HTP.
Anxiety/Panic Disorder

In comparison with studies which investigate the role of serotonin deficiency as a cause of depression, the relationship of serotonin to anxiety and panic disorder has received less attention. However, the outcome of several human studies have shown positive results. Researchers observed an obvious decrease of symptoms in patients who supplemented with 5-HTP\textsuperscript{12,13}. This would be expected, because serotonin deficiency has been associated with agitated depressions, whose symptoms include pacing, tremulousness, irritability, aggressive behaviors, and obsessional thinking. On the other hand, anhedonic depression (lack of energy and loss of an ability to enjoy pleasurable activities) has been more associated with a deficiency of norepinephrine which is made from the amino acid tyrosine.

Sleep Disorders

Melatonin, which helps regulate the sleep-wake cycle, is a metabolite of serotonin (see Figure 1). Several studies suggest that 5-HTP improves sleep patterns by improving the synthesis of melatonin\textsuperscript{14,15,16,17}. As noted in Figure 1, in order for serotonin to be made into melatonin, pantetheine (Vitamin B\textsubscript{5}, a precursor to acetyl Co-A) is required to facilitate the conversion to acetylserotonin. The next step requires methionine, a precursor to S-adenosylmethionine (SAM). Consequently, pantetheine and methionine are often given at bedtime along with 5-HTP and Vitamin B\textsubscript{6} to facilitate melatonin synthesis and sleep.

Weight Management

In a six-week clinical study with obese patients, those who supplemented with 5-HTP were able to reduce carbohydrate intake, which contributed to significant weight loss\textsuperscript{18}. By increasing the availability of serotonin, a noticeable suppression of appetite was accomplished, thereby providing a feeling of satiety. Specifically, 5-HTP was found to reduce appetite by its actions on specific subtypes of serotonin receptors (5-HT-1 and 5-HT-2) in rats\textsuperscript{19}. Other studies showed that 5-HTP strongly suppresses appetite for three days after dosing\textsuperscript{20}. Further work demonstrated that rats which were given 5-HTP not only ate less, but also reduced the number of meals and ate more slowly\textsuperscript{21}. A double-blind study suggested that the appetite-suppressive effects could be attributed to decreased consumption of carbohydrates\textsuperscript{22}. Since the hyperinsulinemic (insulin resistance) effects of carbohydrates are undoubtedly the main cause of obesity\textsuperscript{23,24}, and carbohydrates cause the release of serotonin (“sugar haze” effects), then it is not surprising that the restoration of deficient levels of serotonin by natural means with 5-HTP would decrease carbohydrate cravings.

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Fibromyalgia

In one study, four different approaches were used to address pain from fibromyalgia: 1) monoamine oxidase inhibitors (MAOIs); 2) tricyclic antidepressant medication (amitriptyline); 3) MAOIs and 5-HTP together; and 4) 5-HTP alone. The results from the four groups were compared to determine their effects on pain in patients suffering from fibromyalgia\textsuperscript{25}. In another study, the combination of MAOIs and 5-HTP showed the most impressive results. 5-HTP alone was also found to be effective in reducing the number of tender points, anxiety, pain intensity,
fatigue, and in improving the quality of sleep (p < .01) during a 90-day open trial)\textsuperscript{26}.

Migraine

5-HP has been shown to have a beneficial effect equivalent to methysergide (a medication for migraine)\textsuperscript{27}. Another double-blind, placebo-controlled study\textsuperscript{28} showed a significant effect of 5-HTP on migraine. In a third study, 5-HTP had a beneficial effect on migraine, but propanolol (a drug) did better, and the combination of propanolol and 5-HTP did the best\textsuperscript{29}. 5-HTP has been noted in all studies to not have the side effects found with medication.

Summary

5-hydroxytryptophan (5-HTP) shows great promise in the treatment of depression, anxiety and panic disorders, obesity, sleep disorders, migraine, and fibromyalgia. Few side effects have been reported, and they were generally mild and tended to occur when 5-HTP was coadministered with antidepressant drugs. 5-HTP is available over-the-counter as an extract from the natural legume, \textit{griffonia simplicifolia}. It should be taken with Vitamin B\textsubscript{6} during the day to help restore serotonin and with Vitamin B\textsubscript{6}, Vitamin B\textsubscript{5} (pantethine), and methionine at night to restore deficient melatonin levels for sleep.

Safety

Recent concerns expressed by the Mayo Clinic about 5-HTP are puzzling\textsuperscript{30}. This plant extract is not a fermentation product like tryptophan and would not be expected to have any contaminants implicated as the cause of Eosinophilia Myalgia Syndrome (EMS), which led to the ban on tryptophan years ago. Rather, the possibility that 5-HTP could eventually be recognized as a safer, more effective treatment for serotonin and melatonin deficien- cy disorders (thus rendering most antidepressant medication obsolete) may be the issue. Nevertheless, all retailers and prescribers should insist on having assays on all 5-HTP-containing products to be certain that “peak X” is not found\textsuperscript{**}. One hopes that economic factors will be put aside in favor of good science and a dedication to provide safer, effective help for the patients we serve.

Deficiencies of serotonin and/or melatonin are related to various conditions, including depression, anxiety, panic disorder, sleep disorder, weight problems, and fibromyalgia. 5-HTP has been shown to help these conditions.

Do not use 5-HTP with MAO inhibitors or other antidepressants unless recommended by your doctor.

\textsuperscript{**} “Peak X” is the unknown contaminant in a batch of tryptophan from a Japanese manufacturer which is believed to have caused the Eosinophilia/Myalgia Syndrome (EMS) several years ago.
Kynurenic Acid (urine) → Tryptophan → Nicotinamide Adenine Dinucleotide (NAD) → Tryptophan hydroxylase → Biopterin H₂ → 5 HTP (5-Hydroxy-Tryptophan) → Pyridoxal-5-Phosphate (VIT B₆) → Serotonin → MAO → Acetyl CoA → Pantethine (B₃) → N-Acetyl Serotonin → S-adenosyl methionine (SAM) → SAH → Melatonin
NARRATIVE FOR FIGURE 2  
NORMAL NEURON AND SYNAPTIC PHYSIOLOGY

The 100+ billion neurons (brain cells) communicate through synaptic connections (up to 10,000 synapses per neuron), which calculates to potentially one quadrillion (1,000,000,000,000,000) synapses in the brain. Each of these one quadrillion or so synapses is an exemplary microcosm of physiological homeostasis which happens everywhere in the brain and body. Each synapse balances its potentially thousands of packets of neurotransmitters with potentially millions of molecules per packet so that there is just the right amount of neurotransmitter activity needed to maintain homeostasis. In other words, in order for me to write this information at this moment and for you to read and comprehend it, “oodles and oodles” of neurotransmitter molecules in our brains are continuously regulated by homeostatic mechanisms. Neurotransmitters are continuously being synthesized, transported, stored, released, recycled, regulated and destroyed within us so that sensory perception, thinking and cognition, memory storage, attention and concentration, behavior and emotion can happen!

Synthesis, Storage, Release and Reuptake of Neurotransmitters (steps 1-8 in figure):
1) Nutrients are delivered via the arterial blood flow to the neuron.
2) Waste products and toxins are carried away by venous blood flow, to be filtered by the liver and kidneys and excreted.
3) Neurotransmitter molecules are constructed in the cytoplasm of the neuron cell body.
4) Neurotransmitters are transported through the axon (communication conduit) to the presynaptic (before the synapse) bouton (swelling) at the end of the axon.
5) Neurotransmitters are stored in packets awaiting release into the synapse.
6) When the signal arrives from the presynaptic cell body (at top of figure), neurotransmitters are released into the synapse.
7) The neurotransmitters released from the presynaptic neuron, float across the synapse and fit into sites on the membrane of the next postsynaptic neuron designed for the molecular structure of the neurotransmitter (i.e., a molecular key fitting into a molecular keyhole to unlock a molecular lock). This sets off a reaction in the postsynaptic neuron which can pass on the information through its cell body on to the next neuron, and so forth.
8) Finally, the neurotransmitter molecule can break free of its receptor site, float back across the synapse, and be recycled by the presynaptic neuron to be released again later.

Regulation of Neurotransmitters (steps A-H in figure).
A) Postsynaptic upregulation. If the receptor sites on the postsynaptic neuron are not stimulated enough by neurotransmitters, the “hungry” neuron will grow more receptor sites in order to capture as much neurotransmitter as possible.
B) Postsynaptic downregulation. If there is too much stimulation of the postsynaptic receptor sites (from neurotransmitters or drugs), the “overstuffed” postsynaptic neuron will grow fewer receptor sites in order to avoid excessive stimulation.
C) Normal postsynaptic regulation. If there is a sufficient supply of neurotransmitter, the “satisfied” postsynaptic neuron grows a normal amount of receptor sites. This is homeostasis, or a balanced state.
D) Autoreceptor sites. The presynaptic neuron (neuron which makes and releases neurotransmitters) has receptor sites on itself! These sites sense when there is too much or too little neurotransmitter present and immediately call for a correction.
E) Enzymes are released by neurons into the synapse in order to break down (catabolize) excessive neurotransmitters. Neurotransmitter molecules must journey across a minefield of enzymes to get to receptor sites.
F) The reuptake process (#8 above) is regulated according to the supply of and demand for neurotransmitter.
G) Long-term intracellular adaptation occurs within the postsynaptic neuron in order to find the best possible state of homeostasis regardless of the neurotransmitter availability or artificial drug effects. The neuron does the best it can with the resources it has been given.
H) Long-term adaptation occurs within the presynaptic neuron regardless of its nutrient availability, drug or toxin effects, stimulation from previous cells on its dendrites, and/or other factors.
Figure 2

Normal Neuron & Synaptic Physiology

- **A** Post synaptic up regulation
- **B** Post synaptic down regulation
- **C** Post synaptic homeostasis

- **1** Amino Acids, Vitamins, Minerals, Lipids Delivered
- **2** Waste Products and Toxins Removed
- **3** Information Flow
- **4** Information Flow
- **5** Information Flow
- **6** Information Flow
- **7** Information Flow
- **8** Information Flow

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