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REVIEW

5-HTP efficacy and contraindications

Marty Hinz[1]
Alvin Stein[2]
Thomas Uncini[3]

[1]Clinical Research, NeuroResearch Clinics, Inc, Cape Coral, [2]Stein Orthopedic Associates, Plantation, FL, USA; [3]University Medical Center Mesabi Hibbing, MN, USA

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Abstract: L-5-hydroxytryptophan (5-HTP) is the immediate precursor of serotonin. It is readily synthesized into serotonin without biochemical feedback. This nutrient has a large and strong following who advocate exaggerated and inaccurate claims relating to its effectiveness in the treatment of depression and a number of other serotonin related diseases. These assertions are not supported by the science. Under close examination, 5-HTP may be contraindicated for depression in some of the very patients for whom promoters of 5-HTP advocate its use.

Keywords: 5-HTP, 5-hydroxytryptophan, L-5-HTP, L-5-hydroxytryptophan

Introduction

In the United States, the nutritional supplement 5-hydroxytryptophan (5-HTP) became available over the counter in April of 1995.[1] Previously, it was only available by prescription. Its intuitively seductive appeal has encouraged its increasing use while disregarding the actual science which stands in sharp contrast to the general perceptions of the public and many physicians.[2–15]

The argument for using 5-HTP

When placed in the proper context, the following basic chemical properties[2–15] explain the failure of 5-HTP to achieve consistent results. The following scientific facts are generally accepted without dispute:

- In central nervous system disease states associated with synaptic serotonin dysfunction, synaptic serotonin levels in the brain must be increased to induce optimal outcomes.
- Serotonin does not cross the blood–brain barrier.
- 5-HTP freely crosses the blood–brain barrier.
- 5-HTP is freely converted to serotonin without biochemical feedback inhibition.
- When infinitely high amounts of 5-HTP are administered, it is theoretically possible to achieve infinitely high levels of serotonin. One limiting factor is the availability of the enzyme L-aromatic amino acid decarboxylase (AAAD), which freely catalyzes the conversion of 5-HTP to serotonin.

The basic facts listed above form the basis of a very appealing and vehemently defended scenario, "5-HTP is all that is needed when levels of serotonin need to be increased effectively and safely." Inadequate levels of serotonin in the brain have been associated with numerous disease states and here is a nutrient that can theoretically raise serotonin levels as high as needed.[16–18]

Correspondence: Marty Hinz
1008 Dolphin Drive, Cape Coral, FL 33904, USA
Tel +1 218 626 2220
Fax +1 218 626 1638
Email marty@hinzmd.com

Short-term efficacy of 5-HTP alone

Generally, efficacy studies related to 5-HTP fall into one of two categories: open (nonblinded) and double-blind, placebo-controlled studies. One naturopathic physician, who is considered by some to be a 5-HTP expert,[17] interprets the results from an open study on his web site as follows:[18] He reported one of his more impressive studies that involved 99 patients who were described as suffering from therapy resistant depression. These patients had not responded to any previous therapy including all available antidepressant drugs as well as electro convulsive therapy. Specifically reported was, "These therapy resistant patients received 5-HTP at dosages averaging 200 mg daily but ranging from 50 to 600 mg per day. Complete recovery was seen in 43 of the 99."[18]

There are two points that require further discussion. First, the naturopath claims that only 5-HTP was administered to patients in the study.[18] A review of the entire study revealed that a combination of 5-HTP with carbidopa was administered.[19] Carbidopa is a general decarboxylase inhibitor that inhibits peripheral synthesis of the centrally acting monoamines (serotonin, dopamine, norepinephrine, and epinephrine). It affects the response to 5-HTP dosing values by significantly increasing the availability of 5-HTP in the central nervous system.[10] A comprehensive literature search of the use of 5-HTP for treating depression revealed that administration of 5-HTP alone is not very effective. To compensate for this efficacy problem, 5-HTP is often used in combination with other drugs and/or substances. There are more published studies examining the use of 5-HTP in combination with another substance than the use of 5-HTP alone.

Second, according to the naturopath's web site, 43 of 99 (43.4%) subjects taking 5-HTP and carbidopa achieved relief of depression.[18] The web site notes that "such significant improvement in patients suffering from long-standing, unresponsive depression is quite impressive…"[18] This illustrates a second flaw: this magnitude of improvement is no greater than that of a placebo.

Double-blind, placebo-controlled studies of depression have consistently revealed that the placebo effect after 30 days of depression treatment ranges from 30%–45%.[13] It is inaccurate to describe the referenced study as "One of the more impressive studies…"[18] when the efficacy rate was only 43.4%. This statement reveals a lack of understanding of the complex and large impact the placebo effect has in treating patients with depression.[13] A review of peer-reviewed studies does not support the effectiveness of 5-HTP as follows:

1. "Trials performed do not provide evidence for an antidepressant effect of 5-HTP."[20]
2. 2009 meta-analysis of 111 (one hundred eleven) 5-HTP / depression studies concluded, "Further studies are needed to evaluate the efficacy and safety of 5-HTP and tryptophan before their widespread use can be recommended."[21]
3. "While there is evidence that precursor loading may be of therapeutic value, particularly for the serotonin precursors 5-HTP and tryptophan, more studies of suitable design and size might lead to more conclusive results."[22]
4. "The immediate serotonin precursor, 5-HTP, has been given to depressed patients either alone or in combination with a MAO inhibitor. The results are conflicting and, in the main, do not provide convincing evidence for an antidepressant effect for 5-HTP."[23]

While there are some published pilot studies relating to small groups of subjects, the majority of these smaller studies conclude by noting that more studies are needed. The peer-reviewed literature supports the assertion that use of 5-HTP alone in the management of depression is associated with efficacy no greater than placebo and that its use is controversial.[19–23]

While those strongly advocating the use of 5-HTP alone believe that depression is due to serotonin dysfunction, depression may also be associated with catecholamine dysfunction, including dopamine and/or norepinephrine, or a combination of serotonin and catecholamine dysfunction.[24,25] Administration of 5-HTP alone facilitates depletion of dopamine, norepinephrine, and epinephrine (see Discussion). When catecholamine neurotransmitter levels influence depression, administration of 5-HTP alone is contraindicated since it may deplete dopamine and norepinephrine, thereby worsening the disease and its underlying cause. This contraindication is not exclusive to depression, but extends to all other disease processes for which dysfunction of a catecholamine component has been implicated, including attention-deficit hyperactivity disorder (ADHD),[26] seasonal affective disorder,[27] obesity,[28] generalized anxiety disorder,[25] and Parkinson's disease.[29]

5-HTP alone contraindicated for long-term use

The most significant side effects and adverse reactions may occur with long-term use (many months or longer). Administration of 5-HTP alone depletes catecholamines (dopamine, norepinephrine, and epinephrine).[12,15] When dopamine depletion is great enough, 5-HTP will no longer function.[15] If other centrally acting monoamine-related

disease processes involving catecholamines are present, administration of 5-HTP alone may deplete dopamine, norepinephrine and epinephrine thereby exacerbating these conditions.[15]

Based on monoamine transporter optimization (MTO) studies, managing depression and other centrally acting monoamine-related diseases requires a combination of properly balanced dopamine and serotonin amino acid precursors.[2–15]

Synthesis of serotonin from 5-HTP and dopamine from L-dopa is catalyzed by the same enzyme, L-aromatic amino acid decarboxylase (AAAD). Dopamine and serotonin amino acid precursor administration must be in proper balance. If only 5-HTP or 5-HTP that dominates dopamine at the enzyme is administered, it will block dopamine synthesis at the AAAD enzyme through competitive inhibition, leading to depletion of dopamine and the rest of the catecholamines.[6,9,12,15,30]

Metabolism of serotonin and dopamine is catalyzed by monoamine oxidase (MAO). The activity level of MAO is not static. With increasing doses of 5-HTP, which lead to increased serotonin levels, MAO activity increases. Without a properly balanced increase in dopamine there will be increased metabolism of dopamine leading to depletion.[1,3,4,6,9,12,15]

The synthesis, metabolism, and transport of serotonin and dopamine, along with their amino acid precursors, are primarily controlled by the functional status of transporters which is carried out by organic cation transporters (OCT). Serotonin, dopamine, and their amino acid precursors must be transported by OCT across cell membranes. Transport dominates, controls and regulates synthesis and metabolism. Administration of 5-HTP alone leads to increased unbalanced transport of serotonin. Competitive inhibition at the transporters will inhibit movement of dopamine and its precursors into areas that affect synthesis and metabolism, compromising and depleting dopamine (catecholamine) levels. Long-term administration of 5-HTP alone or in an unbalanced manner, facilitates depletion of catecholamines, negatively affecting neurotransmitter-related disease processes.[3–15,31]

Use of 5-HTP with a general decarboxylase inhibitor

A literature review revealed that more studies have been reported using 5-HTP in combination with another substance than using 5-HTP alone due to the lack of efficacy of 5-HTP alone. One combination examined includes the use of 5-HTP with carbidopa. Carbidopa inhibits peripheral conversion of 5-HTP to serotonin and L-dopa to dopamine.[32] Carbidopa was originally used in combination with L-dopa to control symptoms associated with serotonin and dopamine imbalance that occur when only L-dopa was administered to manage Parkinson's disease. The following problems have been reported with use of carbidopa to treat Parkinson's disease.[10]

- "Most of the side effects observed in the management of Parkinson's disease with the combination L-dopa and carbidopa are attributed to the carbidopa."[10,15]
- "Due to the lack of specificity of L-aromatic amino acid decarboxylase, 5-HTP administration results in 5-HT (serotonin) production in dopaminergic as well as in serotonergic neurons."[23]

Additionally, a previous study reported that in animals 5-HTP caused increased turnover of both dopamine and norepinephrine. They hypothesized that 5-HTP is taken up by catecholaminergic neurons, transformed into 5-HT that, in turn, could act as a false transmitter, possibly increasing the turnover of catecholamines. "The net functional result of these two opposite processes, ie, formation of a false transmitter and decreased synthesis of catecholamines, is unknown. In other words, it is unknown whether 5-HTP augments or reduces catecholaminergic neuronal functions."[26]

Monoamine depletion by amino acid precursors

Serotonin and dopamine systems exist in two distinctly different and separate states. The endogenous state occurs when no supplemental amino acid precursors (Figure 1) are administered. The competitive inhibition state occurs when at least one serotonin and one dopamine amino acid precursor (Figure 1) are administered simultaneously. Competitive inhibition states have been described for many years, but until the publication of MTO technology, this competitive inhibition was considered to be "probably meaningless."[12,14,30] Competitive inhibition occurs during the balanced and unbalanced state. In the unbalanced state, amino acid precursors of serotonin or dopamine dominate the opposite system in synthesis, metabolism, and transport, leading to depletion of nondominant monoamine neurotransmitters (Figure 2).[3,6–15]

Numerous studies published since 2009 document the need to administer serotonin amino acid precursors simultaneously in proper balance with dopamine precursors in order to prevent depletion (Figures 1 and 2).[2–15]

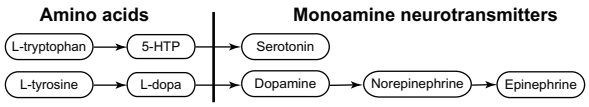

Figure 1 Synthesis pathway of serotonin and catecholamines.
Abbreviation: 5-HTP, 5-hydroxytryptophan.

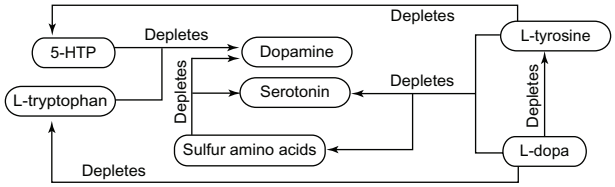

Figure 2 When an amino acid precursor of serotonin or dopamine is administered alone or in a manner that dominates the synthesis, metabolism, and/or transport of the other system, depletion may occur.[12–15]
Abbreviation: 5-HTP, 5-hydroxytryptophan.

Specific examples of a dominant monoamine depleting a nondominant monoamine and/or amino acid precursor are listed here and illustrated in Figure 2.

- 5-HTP may deplete dopamine.[33–37]
- L-tryptophan may deplete dopamine.[35]
- L-dopa may deplete serotonin.[2–15,38–42]
- L-dopa may deplete L-tryptophan.[42]
- L-dopa may deplete L-tyrosine.[42]
- L-dopa may deplete sulfur amino acids.[4,6,43–45]
- L-tyrosine may deplete serotonin.[46,47]
- L-tyrosine may deplete 5-HTP.[47]
- L-tyrosine may deplete sulfur amino acids.[4,6,43–45]
- Sulfur amino acids may deplete dopamine.[48]
- Sulfur amino acids may deplete serotonin.[49]

Effects of 5-HTP when administered in an unbalanced manner

Amino acid precursors of serotonin and dopamine in the competitive inhibition state are intertwined during synthesis, metabolism, and transport to the point that they function as one system. This is a deep-seated interaction as discussed in the novel concept of a vital regulatory super system (APRESS), published in 2011. The paper discusses how the serotonin and dopamine systems, when properly balanced in the competitive inhibition state, function as one system. In this state, functions regulated only by serotonin in the endogenous state can be regulated by manipulating dopamine levels and functions regulated only by dopamine in the endogenous state can be regulated by manipulating serotonin.[12]

Improperly balanced administration of serotonin and dopamine precursors (Figures 1 and 2) leads to decreased efficacy and increased incidence of side effects. Most importantly, if only one precursor of the serotonin and dopamine system is administered or it is administered in a manner that dominates the other system (either serotonin or dopamine) in synthesis, metabolism and transport, neurotransmitter depletion of the dominated system will occur. When this depletion of the nondominant system is great enough, any effects observed with administration of the single or dominant amino acid will no longer be observed. An amino acid precursor no longer functioning can be observed in the management of Parkinson's disease in which the effects of L-dopa are no longer observed over time due to serotonin depletion.[7–15]

A study involving properly balanced serotonin and dopamine amino acid precursor dosing values guided by MTO published in 2009 and 2010 documents that administration of properly balanced serotonin and dopamine precursors is not only highly effective for managing depression, but can also be used to differentiate bipolar depression cycling heavily on the depressive side from unipolar depression (major affective disorder).[6] Proper balancing of serotonin and dopamine amino acid precursors, which can only be optimized using MTO, is critical.[2–15]

Administration of 5-HTP in a properly balanced manner

To achieve optimal efficacy, minimal side effects, and prevent depletion of other amino acids and neurotransmitters, 5-HTP must be administered in proper balance with dopamine amino acid precursors along with proper levels of sulfur amino acids.

Synthesis and metabolism are controlled by transporter function. Transporters move serotonin, dopamine and their amino acid precursors into and out of cells to sites where synthesis and metabolism occur. Most important is the transporter's ability to establish specific levels of serotonin and dopamine in numerous locations, including the synapses between pre- and post-synaptic neurons.[12,15,31]

MTO is an in situ method for determining the functional status of OCT responsible for establishing serotonin and dopamine levels throughout the body. Optimization requires establishing serotonin in the Phase 3 optimal range while dopamine is in its Phase 3 optimal range. The Phase 3 optimal ranges of serotonin and dopamine are independent of one another. When both serotonin and dopamine are in their respective phase 3 optimal ranges, optimization has occurred.[5,7,10,11,13,15]

Optimal group results cannot be obtained without MTO. The following are group effective therapeutic ranges defined by MTO during simultaneous administration of serotonin and dopamine precursors:

- 5-HTP daily dosing values > 0 to 2,400 mg per day.[14,15]
- L-tyrosine daily dosing values > 0 to 14,000 mg per day.[14,15]
- L-dopa daily dosing values > 0 to 2,100 mg per day.[14,15]

The effective therapeutic ranges listed above are independent of each other. For example, in one patient, a daily 5-HTP dosing value of 2,400 mg per day with an L-dopa dosing value of 30 mg per day may be required for proper balance of transport to place both serotonin and dopamine in their respective Phase 3 optimal ranges. Another patient may require 25 mg per day of 5-HTP with 2,100 mg of L-dopa for Phase 3 optimization. Dosing values required for transporter optimization are highly individualized.[15]

To understand the extreme variability in the dosing levels of 5-HTP and the other amino acid precursors, it is important to understand why these transporters react so differently from one individual to the next. Neurotransmitters facilitate the flow of electric signals across the synapse between the pre- and post-synaptic neurons. When a change in the overall flow of electricity across the synapse is needed, a signal is sent throughout the body that encodes the identical transporters to regulate and control neurotransmitter flow in the specific manner required to optimize this flow. When permanent damage from neurotoxins, trauma, biologicals, and/or genetic predisposition occurs to postsynaptic neurons, the electrical flow that regulates function is compromised. This process may damage areas regulating affect and mood, leading to depression. With this sequence of circumstances, a signal goes out encoding the OCT2 to increase or decrease synaptic levels of serotonin and/or dopamine in order to compensate for the electrical deficit being experienced across the synapse.[2,13–15,31]

Since serotonin and dopamine do not cross the blood–brain barrier, the total number of serotonin and dopamine molecules present in the brain is a function of the amount of nutrients (amino acid precursors) available to be synthesized into new neurotransmitter molecules. If the amount of neurotransmitter molecules is low or inadequate, a relative nutritional deficiency exists. Inadequate monoamine levels can only be elevated to levels required for optimal transporter function through administration of supplemental nutrient precursors guided by "monoamine transporter optimization" (MTO).[15]

Optimal efficacy and minimized side effects are not a function of achieving sufficiently high amino acid dosing levels; they are a function of achieving a proper balance between serotonin and dopamine.[2–15]

Conclusion

5-HTP in the treatment of depression has languished for years. Intuitively, the potential is extraordinary, but from a practical level efficacy is no better than placebo. In review of the science, effective integration of 5-HTP into a patient management plan is much more complicated than simply giving some 5-HTP in order to have more serotonin throughout the system.

Administration of 5-HTP alone is contraindicated for depression and any process involving a catecholamine component due to its ability to facilitate depletion of these neurotransmitters. 5-HTP should be administered carefully in patients because depletion of dopamine and norepinephrine may exacerbate existing disease processes or precipitate onset of catecholamine-related problems.

Administering serotonin or dopamine amino acid precursors should never involve administration of only one amino acid. Improperly balanced amino acid precursors are associated with decreased efficacy, increased side effects, and depletion of the codominant system.

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