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5-Hydroxytryptophan plus SSRIs for interferon-induced depression: Synergistic mechanisms for normalizing synaptic serotonin

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Summary Interferon-α (IFN) is widely used in the treatment of certain cancers and viral infections, including hepatitis C (HCV). Unfortunately, depression is a common side effect of IFN therapy, affecting approximately a third of HCV patients receiving IFN therapy. Studies have shown that selective serotonin reuptake inhibitors (SSRIs) can effectively treat IFN-induced depression in only 63–75% of cases. For the remaining percentage, depression often necessitates dose reduction of or discontinuation from IFN therapy. Emerging evidence indicates that IFN may cause depression by affecting brain serotonin. IFN has been shown to increase serotonin reuptake and to decrease serotonin synthesis. We hypothesize that SSRIs are not fully effective because they affect only serotonin reuptake, not serotonin synthesis, and that effective treatment must address *both* uptake *and* synthesis. 5-Hydroxytryptophan (5-HTP) effectively increases central nervous system synthesis of serotonin. It is the immediate precursor of serotonin and is widely available as a dietary supplement, which is well absorbed after an oral dose. Several double-blind studies have shown 5-HTP to be effective in the treatment of nondrug-induced depression. We hypothesize that patients who become depressed on IFN will respond to the synergistic combination of SSRIs plus 5-HTP.

Introduction

Interferon-α (IFN) is first-line treatment for a number of diseases, including hepatitis C (HCV). Unfortunately, depression is a common side effect of IFN therapy, which prevents many patients from com-

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pleting or even attempting IFN therapy. This article reviews the medical literature supporting the hypothesis that IFN induces depression by disrupting the brain serotonin system through at least two different mechanisms. We then propose a novel treatment strategy targeting these mechanisms, involving combination therapy with a serotonin reuptake inhibitor and 5-hydroxytryptophan (5-HTP).

Interferon-induced depression is a significant problem

In the United States alone, an estimated 3—4 million individuals are infected with the hepatitis C virus (HCV) [1] (nearly 2% of the total US population, making hepatitis C more prevalent than HIV). Worldwide, approximately 160 million people are infected [2]. Of those with HCV in the US, 25—30% receive treatment [3]. To date, interferon-α (IFN) [1] is the only FDA-approved treatment for HCV [4]. IFN is also used in the treatment of malignant melanoma, hairy cell leukemia, chronic myeloid leukemia, and AIDS-related Kaposi's sarcoma [4]. According to IMS America, 60,000 prescriptions for IFN are filled each month [2].

Unfortunately, IFN induces neuropsychiatric side effects consistent with a Major Depressive Episode: depressed mood, fatigue, lethargy, cognitive impairment [5] and impairment in social and occupational functioning [5]. Suicide attempts and completed suicides have also been linked to IFN treatment [6].

A recent study reported that IFN-induced depression developed in 33% of IFN-treated HCV patients, all of whom had been free of active psychiatric illness for at least 6 months before treatment initiation [7]. Other studies have reported a 27—35% incidence of depression among patients who have recently begun treatment involving IFN [8,9]. One study of 96 patients found that, after beginning IFN therapy, all of the patients developed or showed an increase in depressive symptoms [10]. It has been estimated that depression necessitates dose reduction in 40% of IFN-treated patients and that 15% of patients drop out of IFN treatment due to depression [11].

[1] In many formulations of interferon, it is combined with ribavirin. Interferon-α is also available in a variety of forms. The newer, pegylated forms, such as peginterferon α-2b (PEG-Intron®) and peginterferon α-2a (Pegasys®), are probably the most common at this time.

Consistent with the human evidence of a link between IFN and depression, rats treated with IFN and evaluated with the forced swim test [12] showed increased immobility time, predictive of increased liability for depression in humans. In addition, there was a positive dose—response relationship between IFN and immobility time [13].

Current treatments: serotonin reuptake inhibitors

Most studies of treatments IFN-induced depression have involved the class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) [7,9,14,15]. Although these studies suggest that SSRIs are a promising treatment for IFN-induced depression, it is not clear what the true response rate will eventually prove to be. Of these studies, only one used a double-blind placebo-controlled design [9]. Extrapolating from that small prophylactic study, one might estimate an SSRI failure rate of approximately 25%. The true SSRI failure rate may prove to be higher. In a meta-analysis of 36 clinical trials of patients with (non-drug-induced) depression, 37% of patients failed to respond to SSRIs [16].

Pathophysiology of IFN-induced depression

IFN increases synaptic serotonin reuptake

Emerging evidence indicates that IFN increases serotonin reuptake and the transcription rate of serotonin transporter mRNA [17]. The increase in serotonin reuptake would therefore be expected to decrease synaptic serotonin, decrease serotonin neurotransmission, and lead to depression. SSRIs, by definition, inhibit serotonin reuptake. Because the effect of SSRIs on serotonin reuptake is opposite to that of IFN, there is good scientific rationale for their use in IFN-induced depression. Why, then, should SSRI therapy not be consistently efficacious? We believe that SSRIs address only part of the pathophysiology of IFN-induced depression.

IFN reduces serotonin synthesis

The metabolic precursor to serotonin is tryptophan. However, only a small percentage of tryptophan is available to the serotonin pathway;

approximately 90% is catabolized along the competing kynurenine pathway [18]. This pathway is controlled by the enzyme indoleamine 2,3-dioxygenase (IDO) [19]. IFN induces this enzyme, as evidenced by increases in IDO mRNA expression [20], in plasma kynurenine [21], and in the plasma kynurenine-to-tryptophan ratio [22].

Because IFN increases the amount of tryptophan metabolized along the competing kynurenine pathway, correspondingly less tryptophan is available to the serotonin pathway (see Fig. 1). IFN-induced reductions in serotonin synthesis have been observed in both animals and humans. In rats, IFN administration has been found to significantly reduce, in a dose-dependent manner, serotonin in the frontal cortex, midbrain, and striatum [23]. In humans, IFN treatment has been found to significantly reduce plasma serotonin [22].

Several studies have shown that reducing serotonin synthesis by depriving the brain of tryptophan induces depression within hours [24—26]. It has been hypothesized that IFN induces depression by a related mechanism [19,22,27], diagrammed in Fig. 1. Although other neurotransmitters, notably catecholamines, are involved in mood regulation, these studies suggest that normal mood depends in large part on normal serotonin stores.

Serotonin precursor: 5-hydroxytryptophan

Influencing serotonin synthesis

Serotonin stores in the CNS cannot be directly influenced, as serotonin in the periphery of the body cannot cross the blood—brain barrier [28]. Additionally, dietary tryptophan cannot significantly impact CNS serotonin levels because IDO is further activated by the increase in tryptophan, leading to a 6-fold increase in the production of kynurenine at the expense of production of serotonin [29].

However, serotonin synthesis can be influenced by intervening at a point in its synthetic pathway that is downstream from tryptophan. The synthesis from tryptophan to serotonin proceeds via the intermediary 5-hydroxytryptophan (5-HTP). 5-HTP can be taken as a dietary supplement and is well absorbed from an oral dose, with about 70% ending up in the bloodstream [30,31]. 5-HTP easily crosses the blood—brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin [32]. Additionally, 5-HTP is not affected by IDO. We therefore propose that the disruption in serotonin synthesis caused by IFN-therapy can be normalized by administering supplemental 5-HTP, as diagrammed in Fig. 2.

Commercial availability of 5-HTP

5-HTP is extracted from the *Griffonia simplicifolia* plant of West Africa. It is typically available as the L-enantiomer, where most of the biological activity resides [33]. L-5-HTP is also known by the synonyms oxitriptan and Ro-0783/B and is available in Europe under various brand names. In the United States, it is commercially available under the Dietary Supplement Health and Education Act of 1994 (DSHEA). As a result, it is exempt from prior FDA approval (in contrast to prescription pharmaceuticals) and is sold directly to the public, in health food stores and other outlets, without prescription.

Efficacy of 5-HTP for non-IFN-induced depression

As a result of the relative lack of regulatory oversight, more definitive, large-scale studies of efficacy and safety have not been conducted for 5-HTP. In conducting our own review of the literature, we were able to identify 27 studies which evaluated the efficacy of 5-HTP for depression (total $N = 990$) (Turner et al., unpublished data; also reviewed by Birdsall [32], Byerley et al. [34] and

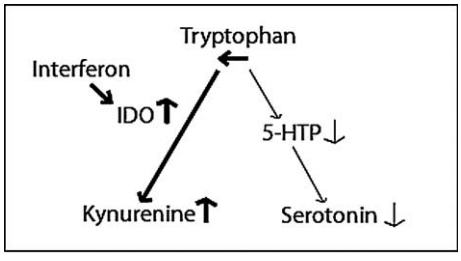

Figure 1 IFN upregulates IDO, diverting tryptophan towards the kynurenine pathway and away from the synthesis of 5-HTP and serotonin.

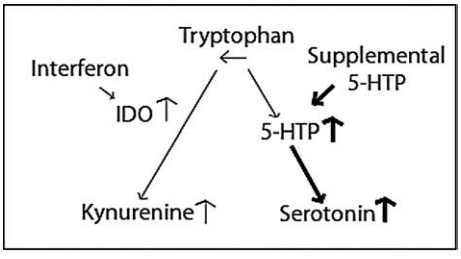

Figure 2 Supplementation with the serotonin precursor 5-HTP should normalize serotonin synthesis despite increased IDO activity.

Shaw et al. [35]). Twelve of these studies were double-blind, placebo-controlled. Unfortunately, in four of these, the authors did not report the placebo response, rendering them uninterpretable. Of the remaining studies, there were five in which 5-HTP was statistically superior to placebo.

Overall, it is difficult to draw any definitive conclusions regarding the efficacy of 5-HTP for depression. However, these results do provide some preliminary evidence for efficacy in non-IFN-induced depression. Because we hypothesize that IFN-induced depression is serotonergically mediated, we anticipate that the response rate to 5-HTP in this population will, if anything, be higher than for depression due to other (possibly heterogeneous) etiologies.

Normalizing serotonin

SSRIs and 5-HTP

IFN appears to induce depression by at least two mechanisms: by increasing serotonin reuptake and by decreasing serotonin synthesis. We hypothesize that, to adequately treat IFN-induced depression, one must normalize synaptic serotonin by both *decreasing* serotonin reuptake and by *increasing* serotonin synthesis. The first can be accomplished with selective serotonin reuptake inhibitors (SSRIs). The second can be accomplished with the dietary supplement 5-HTP, serotonin's immediate precursor. Together, these two interventions should act synergistically (Fig. 3). We therefore propose that IFN-induced depression can be treated with a combination of 5-HTP and SSRI therapy.

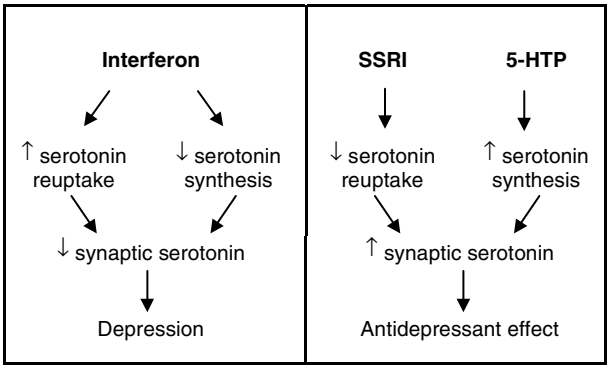

Figure 3 IFN increases serotonin reuptake and decreases serotonin synthesis, leading to decreased synaptic serotonin. To reverse these effects, two medications are needed: SSRIs decrease serotonin reuptake. 5-HTP acts by increasing serotonin synthesis. Together these two should act synergistically to treat IFN-induced depression.

Testing the hypothesis

From the number of studies that have been done and the number of subjects that have been exposed, there is reason to believe that 5-HTP is a safe and effective treatment for depression. However, adequately powered double-blind placebo-controlled trials of 5-HTP for depression are virtually nonexistent. Therefore, not only does the hypothesis that the combination of SSRIs and 5-HTP can treat IFN-induced depression need to be tested, but the hypothesis that 5-HTP is effective and safe for non-drug-induced depression needs to be tested as well. As with any pharmacological intervention, a double-blind, well-controlled trial with an adequate sample size is needed to demonstrate efficacy.

To test this intervention for interferon-induced depression, an effective approach might be to prophylactically treat patients on IFN with SSRIs, and then augment with 5-HTP or placebo in those who become depressed despite the SSRIs. The advantage of this approach is that it limits exposure only to those patients who do not respond to standard treatment, as well as allowing 5-HTP to be tested independently as an augmenting agent.

If a single adequately powered study fails to show that the addition of 5-HTP is not significantly more effective than the addition of placebo, this does not necessarily mean that this hypothesis should be immediately discarded. In large, well-controlled trials submitted by pharmaceutical companies for regulatory approval, drugs eventually approved as antidepressants fail to demonstrate superiority to placebo roughly half of the time [36]. Antidepressant drug trials are thus said to suffer from a lack of assay sensitivity [37]. While there should be some leniency with regard to statistical significance in the first study, it is nevertheless reasonable to expect a statistical trend. Barring any other methodological flaws, such as a failure to include carbidopa (see below), lack of a statistical trend in two consecutive studies should be interpreted as a refutation of the hypothesis.

Co-administration of carbidopa

Another question that needs to be addressed with clinical trials is whether 5-HTP should be given with a peripheral decarboxylase inhibitor. The conversion of 5-HTP to serotonin is regulated by the

enzyme amino acid decarboxylase [38], the same enzyme that regulates the conversion of L-DOPA to dopamine. Patients with Parkinson's disease often receive treatment with Sinemet®, a combination of L-DOPA and the decarboxylase inhibitor carbidopa. By blocking peripheral conversion of L-DOPA to dopamine, more intact L-DOPA traverses the blood–brain barrier and reaches the CNS.

The same rationale exists for administering carbidopa along with 5-HTP. In the absence of carbidopa, peripheral conversion of 5-HTP to serotonin can result in little 5-HTP reaching the CNS. In the presence of carbidopa, this peripheral conversion is blocked. This was demonstrated in a recent study of healthy volunteers in which the addition of carbidopa resulted in a 14-fold increase in 5-HTP plasma levels [39].

Efficacy studies have been conducted both with and without the addition of a peripheral decarboxylase inhibitor (PDI). However, there seems to be no consensus as to whether the addition increases the efficacy of 5-HTP (reviewed in Zmilacher [40]). A study comparing 5-HTP to 5-HTP plus a peripheral decarboxylase inhibitor (PDI) found that GI side effects were dose-dependent and that they occurred more frequently in patients receiving 5-HTP alone. This may be because, in the absence of a PDI, 5-HTP in the periphery is converted to serotonin, causing increased gut motility [41]. Such conversion is blocked by PDIs.

Safety of 5-HTP

Common adverse events

Generally, oral doses of 200–300 mg/day 5-HTP have been well tolerated. The most common side effects of 5-HTP are gastrointestinal (nausea, vomiting, and diarrhea) [34]. GI side effects are usually moderate and often lessen or disappear once a steady dosage is achieved [34]. Less commonly, headache, insomnia, and palpitations can occur [34]. Intravenous administration of 200–300 mg of 5-HTP can induce confusion, memory impairment, and symptoms of behavioral activation (primarily anxiety). These effects are generally much rarer in oral doses, particularly at lower doses [34].

Eosinophilia myalgia syndrome (EMS)

In 1989 and 1990 there was an epidemic of EMS due to ingestion of contaminated L-tryptophan that affected over 1500 people and caused at least thirty eight deaths [42]. These cases sparked fears that 5-HTP might also cause EMS.

In one 5-HTP-implicated case, an HPLC peak was detected and referred to as Peak X. The chemical structure of this contaminant was found to be similar to case-implicated contaminants from L-tryptophan shown to cause EMS [43]. In a 1998 study, 6 commercial preparations of 5-HTP were found to contain Peak X, but at levels between 1/7 and 1/34 of that observed in a case-implicated batch [44]. Some manufactures now test their 5-HTP and claim that it is ''Peak X free''. However, because dietary supplements are regulated differently from drugs in the United States, it is possible that some of the 5-HTP sold to the US public may contain varying quantities of Peak X. This could be a matter of concern to regulatory authorities involved in clinical research, such as the FDA and institutional review boards (IRBs).

However, as of August 1998, the FDA reported that only 10 cases of EMS possibly associated with 5-HTP had been documented worldwide, none resulting in death [42]. No new cases of EMS have since been reported. Also, a recent review questioned the credibility of the above-mentioned reports of Peak X in 5-HTP on methodological grounds [45].

Potential risks of SSRIs and 5-HTP given in combination

Serotonin syndrome is a possible risk with any drug that affects the serotonin system, including not only 5-HTP but also SSRIs and tricyclic antidepressants [46]. Serotonin syndrome is characterized by hypertension, hyperthermia, flushing, hyperreflexia, dizziness, disorientation, and myoclonus [47]. Cases of serotonin syndrome have been reported in patients taking L-tryptophan and fluoxetine together [46] and in patients switching from one SSRI to another [48].

In the case of 5-HTP, a similar syndrome has been reported in dogs that accidentally ingested and overdosed on their owners' 5-HTP [49]. In humans, 5-HTP has been administered in combination with SSRIs and tricyclic antidepressants [50] (including the nonselective serotonin reuptake inhibitor clomipramine [51]), MAOIs [52–54] and tryptophan [55]. To our knowledge, however, serotonin syndrome has not been reported in humans in association with 5-HTP, either as monotherapy or in combination with other medications. In view of the small numbers (total $N \sim 150$) of patients exposed in these studies, these safety findings, although somewhat reassuring, must be regarded

as preliminary. Thus we would advise vigilance to investigators planning research with 5-HTP, either as monotherapy or combination therapy.

Conclusion

Interferon-induced depression is a significant problem with considerable public health consequences. Treating this type of depression will allow more patients to complete treatment for life threatening illnesses, including hepatitis C and certain types of cancer. We have hypothesized here that IFN causes depression via a dual mechanism: by increasing serotonin reuptake and by depleting the substrate for serotonin synthesis. To address these two mechanisms, we propose a combination of SSRI and 5-HTP therapy. SSRIs will block serotonin reuptake, while 5-HTP should restore CNS serotonin synthesis. Together, these interventions should act synergistically to normalize the functioning of the serotonin system and alleviate IFN-induced depression. However, the investigator is advised to exercise caution until the relevant safety issues are more fully understood.

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