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Effects and Side Effects Associated with the Non-Nutritional Use of Tryptophan by Humans[1–3]

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Abstract

The daily nutritional requirement for L-tryptophan (Trp) is modest (5 mg/kg). However, many adults choose to consume much more, up to 4–5 g/d (60–70 mg/kg), typically to improve mood or sleep. Ingesting L-Trp raises brain tryptophan levels and stimulates its conversion to serotonin in neurons, which is thought to mediate its actions. Are there side effects from Trp supplementation? Some consider drowsiness a side effect, but not those who use it to improve sleep. Though the literature is thin, occasional side effects, seen mainly at higher doses (70–200 mg/kg), include tremor, nausea, and dizziness, and may occur when Trp is taken alone or with a drug that enhances serotonin function (e.g., antidepressants). In rare cases, the ''serotonin syndrome'' occurs, the result of too much serotonin stimulation when Trp is combined with serotonin drugs. Symptoms include delirium, myoclonus, hyperthermia, and coma. In 1989 a new syndrome appeared, dubbed eosinophilia myalgia syndrome (EMS), and was quickly linked to supplemental Trp use. Key symptoms included debilitating myalgia (muscle pain) and a high peripheral eosinophil count. The cause was shown not to be Trp but a contaminant in certain production batches. This is not surprising, because side effects long associated with Trp use were not those associated with the EMS. Over 5 decades, Trp has been taken as a supplement and as an adjunct to medications with occasional modest, short-lived side effects. Still, the database is small and largely anecdotal. A thorough, dose-related assessment of side effects remains to be conducted. J. Nutr. 142: 2236S–2244S, 2012.

Introduction

One typically thinks of tryptophan (Trp) as an essential amino acid, with an RDA in the United States of 5 mg/(kg · d), or 0.35 g for a 70-kg individual (1). A typical male consumes ~100 g protein/d (2), or ~1 g/d Trp, because the Trp content of dietary proteins averages ~10 mg/g protein (1). Some people, however, choose to consume additional amounts of Trp as an amino acid supplement. The reason is not nutritional or metabolic, but primarily psychopharmacologic, and the amounts ingested with each use can be many times the amount ingested as a normal component of the diet (i.e., dietary protein). The rationale for this use centers on the discovery, made ~60 y ago, that a product of Trp metabolism, serotonin [5-hydroxytryptamine (5HT)[4]], is a neurotransmitter in the brain (3). Subsequently, 5HT neurons in brain were shown to be involved in brain neuronal circuits that control a variety of functions, including sleep (4) and mood (5). And pharmacologic and physiologic variations in Trp concentrations in the brain were found to modify the rate of 5HT synthesis in and release by neurons (6). The observation that ingesting Trp directly influences brain Trp concentrations and 5HT synthesis suggested potential efficacy for Trp in improving sleep and mood (7,8).

A considerable number of studies have been conducted and published over the past 50 y that have examined the therapeutic

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[4] Abbreviations used: CSF, cerebrospinal fluid; EEG, electroencephalogram; EMS, eosinophilia myalgia syndrome; 5HIAA, 5-hydroxyindoleacetic acid; 5HT, serotonin (5-hydroxytryptamine); LNAA, large neutral amino acid; MAOI, monoamine oxidase inhibitor; REM, rapid eye-movement sleep; SL, sleep latency; SWS, slow-wave sleep; TCAD, tricyclic antidepressant.

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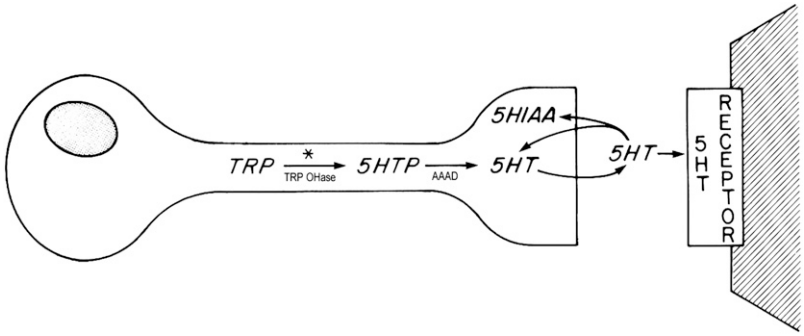

FIGURE 1 Neuronal 5HT synthesis. Trp is hydroxylated to 5HTP, which is decarboxylated to 5HT. Monoamine oxidase initiates the catabolism of 5HT to 5HIAA, the principal 5HT metabolite in the brain. Asterisk indicates the rate-limiting step in 5HT formation, Trp hydroxylation. Adapted with permission from (6). AAAD, aromatic-L-amino acid decarboxylase; 5HIAA, 5-hydroxyindoleacetic acid; 5HT, serotonin (5-hydroxytryptamine); 5HTP, 5-hydroxytryptophan; Trp OHase, Trp hydroxylase.

use of Trp in humans under a number of behavioral and psychiatric conditions, including sleep and mood changes. This literature provides the body of information for assessing the effects and side effects of ingesting moderate to large doses of Trp. The primary focus of this review is on side effects, because Trp has come under considerable scrutiny in relation to the safety of its use, based on the association of Trp ingestion late last century with an often debilitating condition, eosinophilia myalgia syndrome (EMS) (9–11). A review of the symptoms of EMS in the context of Trp use by humans over 5 decades strongly supports the view that EMS was unlikely to have been caused by Trp itself.

Trp and Serotonin

Serotonin is synthesized from Trp in a 2-step reaction (**Fig. 1**). The amino acid is first hydroxylated by the enzyme Trp-5-hydroxylase to 5-hydroxytryptophan, which is then decarboxylated to 5HT by the enzyme aromatic L-amino acid decarboxylase. The initial step is rate limiting and thus the rate of Trp hydroxylation controls the overall rate of 5HT synthesis. When the 5HT biosynthetic pathway was first described, considerable debate revolved around the controls on the activity of Trp hydroxylase, a tetrahydrobiopterin-requiring enzyme (12), and end-product inhibition was a favored mechanism (6). However, the issue was settled by studies showing that physiologic and pharmacologic increases in brain Trp concentrations rapidly stimulate 5HT formation (6). That is, if end-product inhibition were important, such an effect should not have occurred. It is of interest that 5HT synthesis in rat brain could be stimulated by a dose of Trp as low as 12.5 mg/kg (13), a very small dose, suggesting that the pathway is quite sensitive to variations in precursor supply. As it turns out, the brain normally experiences large changes in brain Trp concentrations, such as can occur after the ingestion of a meal, which directly influence 5HT synthesis. An example of this phenomenon is shown in **Figure 2.** In this study, rats deprived of food during the daily light period were given a meal at dark onset, when they normally begin to eat, that differed only in the protein contained in the food. The amount of protein in the food was typical for rats (14). Ingestion of these meals produced marked differences in brain Trp concentrations within a few hours and corresponding changes in the rate of Trp hydroxylation (and 5HT synthesis, because the hydroxylation step is rate limiting in the pathway). It is noteworthy that such dietary effects on 5HT synthesis are accompanied by like changes in neuronal 5HT release (15). This remarkable sensitivity of the 5HT pathway to Trp supply underlies the notion that supplemental Trp might so stimulate 5HT synthesis and release as to produce effects on brain functions, such as sleep.

The Trp hydroxylation rate also depends on the rate of firing of 5HT neurons (16). As a consequence, neuronal firing rate influences the ability of a rise in brain Trp level to stimulate 5HT synthesis. This effect is most easily demonstrated by pharmacologically inhibiting the 5HT neuronal firing rate and observing that an injection of Trp produces a diminished rise in Trp hydroxylation rate (17). Conceivably, when variability is observed in the effect of Trp on a 5HT-linked behavior or physiologic function, differences in 5HT neuronal activity may provide at least part of the explanation. Serotonin is metabolized to 5-hydroxyindoleacetic acid (5HIAA) in a reaction initiated by monoamine oxidase and ultimately exits the brain and is excreted in the urine.

Trp ingestion raises brain Trp levels and stimulates 5HT synthesis in humans, as it does in animals. Brain tissue cannot be directly sampled, but cerebrospinal fluid (CSF) is routinely taken from humans. CSF is a fluid that bathes the surfaces and ventricles

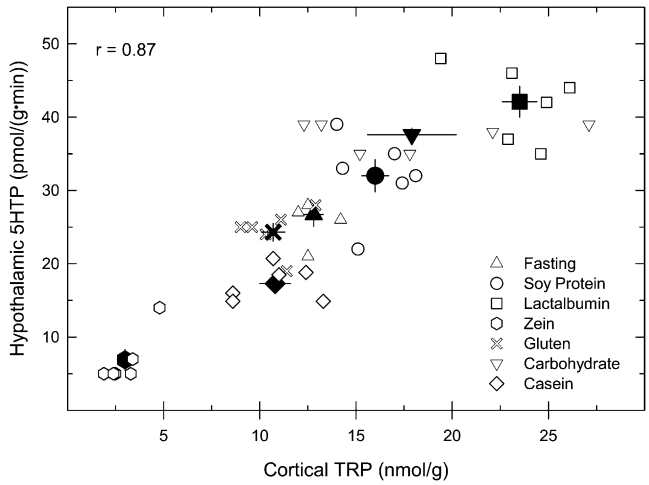

FIGURE 2 Brain Trp concentrations and serotonin synthesis in rats ingesting a single meal containing one of several dietary proteins. On the day of the experiment, food was not available during the daily light period (when rats normally eat little) and was supplied at the onset of the daily dark period (when rats normally begin to eat). Blood and brain samples were obtained 2.5 h into the dark period, after they had consumed a meal and then received a drug to allow 5HT synthesis to be estimated (30 min before killing). See (75) for details. Trp (*x*-axis) was measured in the cerebral cortex (representative of all brain regions); 5HTP (*y*-axis; index of 5HT synthesis) was measured in hypothalamus (and other brain regions). Black symbols represent group means; lines are standard error bars. White symbols are data from individual animals. The dietary protein represented by each symbol is indicated in the figure. $r = 0.87$, $P < 0.001$. Adapted with permission from (75). 5HT, serotonin (5-hydroxytryptamine); 5HTP, 5-hydroxytryptophan.

of the brain, is in equilibrium with brain extracellular fluid, and lies within the blood-brain barrier (18). The concentrations of a variety of solutes have been measured in CSF and taken as a reflection of their concentrations within the brain metabolic compartment. Eccleston et al. (7) administered Trp to participants (50 mg/kg in milk, 3.5 g for a 70-kg individual) and followed blood and CSF Trp concentrations and CSF 5HIAA concentrations for 18 h. CSF 5HIAA levels are often measured in humans and used as an index of 5HT synthesis and/or turnover following some treatments (19). This treatment caused plasma Trp concentrations to rise rapidly, from ~75 nmol/mL to a peak of 600 nmol/mL, a large increase. CSF Trp concentrations rose from ~2.5 nmol/mL to a peak of 15 nmol/mL 6–8 h after Trp ingestion and lagged behind the peak in plasma Trp. CSF 5HIAA concentrations also increased significantly, from a baseline of ~100 pmol/mL to a peak of 200 pmol/mL attained at 8 h. Such findings indicate that Trp ingestion raises Trp concentrations and stimulates 5HT synthesis in human brain. Incidentally, CSF Trp concentrations can also be reduced in human brain and predictably leads to a significant decline in CSF 5HIAA concentrations, suggesting that 5HT synthesis falls when brain Trp declines (19). The treatment is an oral mixture of amino acids that lacks Trp and includes other large neutral amino acids (LNAA). Trp is an LNAA and competes with other LNAA for a shared, competitive transporter across the blood-brain barrier (6). The LNAA include Trp, tyrosine, phenylalanine, leucine, isoleucine, and valine (20,21). Hence, raising plasma levels of the LNAA (other than Trp) reduces Trp transport into the brain and lowers brain (and CSF) Trp concentrations (6,19). Neuronal 5HT production in the human brain thus appears to be sensitive to increases and decreases in Trp supply to brain, as it is in rats.

Effects and Side Effects of Trp in Humans

The most common uses for supplemental Trp by humans are to improve sleep and mood, and many studies published over the past 50 y have focused on these actions.

Mood effects of Trp

A role for 5HT neurons in mood was postulated in the early 1960s and was based in part on observations including the presence of low 5HT and/or 5HIAA levels in the brains of suicide victims and CSF samples from depressed patients, and mood changes following treatment with drugs that lowered (reserpine) or raised [monoamine oxidase inhibitor (MAOI)] neuronal 5HT levels (22,23). The general notion emerged that low brain 5HT function caused or contributed to depressed mood and thus that agents that raised 5HT might elevate mood. Interest quickly developed in the possibility that Trp ingestion might improve mood. Coppen et al. (24) appear to have been the first to explore this possibility by reporting the ability of Trp to enhance the antidepressant potency of a MAOI, with confirmation following soon thereafter (**Table 1**) (25,26). Later studies examined the effects of Trp alone in treating depression, with mixed results: improvement in some cases (27,28), whereas no improvement in others (29,30).

Regarding side effects of Trp treatment, in studies where Trp was given alone, either there was an absence of side effect reporting (27,28,31), side effects were reported to be absent (32), or side effects were observed in some participants (tremor, dry mouth, mild nausea, dizziness) (33). In studies where Trp was administered with an antidepressant drug, side effects attributable to Trp when combined with a tricyclic antidepressant (TCAD; blockers of presynaptic transmitter reuptake/inactivation) were absent (34) or minor (25,33). When Trp was added to a MAOI, side effects were either infrequent-mild (drowsiness, ataxia, muscle twitching) (24,26) or more notable (nausea, drowsiness, hyperreflexia) (25). A similar set of symptoms was also noted by Oates and Sjoerdsma (35) in nonpsychiatric patients receiving an MAOI and Trp (dizzyness-drowsiness-intoxication, muscle clonus-tremor-hyperreflexia, sweating), but not when participants received the same doses of Trp alone (Table 1).

Regarding the relationship of Trp dose to the occurrence of side effects, where no body weight data are provided, we assume a 70-kg body weight, and when D,L-Trp has been administered, that the active principle is L-Trp at one-half the dose specified. For the studies shown in Table 1, 50 mg/(kg · d) L-Trp [one-half of 100 mg/(kg · d) D,L-Trp dose], taken with a TCAD (34) was associated with no side-effects; for a dose of ~85 mg/(kg · d) L-Trp, Rao and Broadhurst (28) did not mention side effects, Jensen et al. (27) noted them to be less than those observed with a TCAD but did not specify what they were, and Chouinard et al. (33) reported side effects of Trp to be tremor, dry mouth, nausea, and dizziness. At 107 mg/(kg · d) [one-half of 214 mg/(kg · d) D,L-Trp dose], taken with a MAOI, Coppen (24) noted drowsiness and occasional ataxia. At about 130 mg/(kg · d) L-Trp, Dunner and Fieve (32) stated that no side effects were present (including neurological findings and lab tests). At doses of ~100 and 200 mg/(kg · d) L-Trp, Pare (25) reported that in combination with a TCAD, side effects were few (occasional nausea, malaise reported) but more frequent in combination with a MAOI (drowsy, nausea, restless, hyperreflexia). For the study by Glassman and Platman (26) where the Trp dose was ~170–250 mg/(kg · d) L-Trp combined with an MAOI, the authors noted simply that side effects "were not frequent." Only 2 studies reported any chemical measurements. In the Wälinder et al. (34) study, plasma Trp rose ~2–3 fold when Trp was added to a TCAD [Trp dose ~50 mg/(kg · d)] and ~2- to 2.5-fold in the Chouinard study [Trp dose ~85 mg/(kg · d)] (33). From this set of data, it is impossible to identify a clear dose above which side effects begin to emerge. It is of interest that the source and thus chemical purity of the Trp used in these studies was rarely specified.

In passing, it should be noted that with the development over the past 30 y and now widespread use of a number of 5HT drugs for treating mood, anxiety, and other disorders, patients can inadvertently find themselves taking more than a single 5HT agent. As a result, a condition has occasionally been observed termed the "serotonin syndrome," which requires medical attention. The symptoms of serotonin syndrome include agitation, delirium, coma, mydriasis, sweating, hyperthermia, tremor, rigidity, and myoclonus (36,37). Precursors (including Trp) are included among the 5HT agents and thus anyone contemplating the use of Trp should do so only after review of current medications.

Sleep effects of Trp

Interest in the link between 5HT and sleep began in the 1960s, initially following observations of sleep perturbations in normal participants (38) and patients given mood-altering drugs that modified neuronal 5HT (39). Later, animal studies examined the impact on sleep of a variety of treatments that modified brain 5HT (4). Broadly speaking, the finding was that drugs or other treatments that reduced 5HT tended to disrupt features of sleep, whereas those that raised 5HT produced the opposite effect (4). Similar observations were made in humans, though with some differences (40,41). In this context, simplistic though it was, it was not surprising to find interest in studying Trp based on the evidence then available showing that Trp administration stimulated 5HT production in the brain (7,8).

TABLE 1 Effect of oral Trp on mood in depressed patients[1]

Patients	Treatment	Effect on plasma Trp	Effects/adverse events	Reference
Depressed (F, M) (n = 25)	DB, PC. MAOI wk 1+2, added DL-Trp [214 mg(kg · d)]; n = 12 or placebo (n = 13) in chocolate milk t.i.d. wk 2. Trp source not specified.	N/M	Antidepressive action of MAOI increased by Trp. Side effects: drowsiness on Trp, occasional ataxia; reported getting first good night's sleep after d 1 of Trp. Depression ratings fell (DB)	24
Depressed (n = 24)	DB. MAOI (n = 14) or TCAD (n = 10) got L-Trp (7.5 or 15 g/d, given t.i.d.) and placebo in random order (n = 14). Length of Trp treatment not specified. Trp source not specified.	N/M	Trp addition improved mood on MAOI, but not on TCAD. Side effects: Trp+TCAD: few side effects (nausea, malaise); Trp+MAOI more frequent, pronounced (drowsy, nausea, tossing, restless, hyperreflexia). Side effects resolved on discontinuing Trp.	25
Depressed (F, M) (n = 20)	DB. MAOI-nonresponsive patients given DL-Trp (0, 12, 15, or 18 g/d t.i.d., 14 d (n = 10/group). Trp source not specified.	N/M	Trp added to MAOI significantly improved mood vs. vehicle. Side effects ``from … Trp and an MAOI were not frequent.''	26
Depressed (n = 8)	DB. L-Trp (8 g/d; n = 8) for 16 d, cross-over to placebo in responders. Trp source not specified.	N/M	Little beneficial effect of Trp. Urinary 5HIAA rose in 7/8. No comment on side effects.	31
Depressed (n = 12)	DB, cross-over. L-Trp (~9 g/d t.i.d.) for 10–18 d. Trp source not specified.	N/M	L-Trp did not improve mood. No side effects, neurological signs, or laboratory abnormalities were noted.	32
Depressed (17 M, 25 F)	DB. L-Trp (6 g/d; Cambrian Chemicals; n = 22) or TCAD (n = 20) for 3 wk.	N/M	L-Trp improved mood comparably to TCAD. Side effects were greater with imipramine than with Trp (not specified).	27
Depressed (n = 16)	DB. L-Trp (6 g/d t.i.d.) or TCAD for 4 wk. Trp source not specified.	N/M	L-Trp and TCAD equally effective in reducing depression. No comment on side effects.	28
Depressed women (n = 24)	DB. 3 wk TCAD + placebo vs. TCAD + dl-Trp [100 mg/(kg · d)] t.i.d.. dl-Trp from Rustan Johansson and Hassle-Ciba-Geigy.	Placebo, 50 nmol/mL; D,L-Trp, 125–175 nmol/mL. CSF Trp 2.5 nmol/mL placebo, 7.5 nmol/mL D,L-Trp.	Greater improvement in depression-anxiety with TCAD+dlTrp than TCAD+placebo. No side effects of dl-Trp.	34
Depressed, 21 F, 4 M	DB. 4 wk: L-Trp/N 2 g/d wk 1, 4 g/d wk 2, 6 g/d wk 3–4, b.i.d. (n = 8). TCAD (n = 8), L-Trp/N + TCAD (n = 9). Trp source not specified.	d 0, 60–70 nmol/mL; d 28, 120–175 nmol/mL, L-Trp/N ± imipramine; d 28, 65 nmol/mL, imipramine.	Trp/N did not improve mood at 4 wk, did not enhance TCAD. Side effects similar for Trp/N and TCAD (tremor, dry mouth, nausea, dizziness in some patients); Trp/N+TCAD mild tremor and dry mouth in most patients.	33

[1] b.i.d., daily dose given in halves; CSF, cerebrospinal fluid; DB, double blind; 5HIAA, 5-hydroxyindoleacetic acid; MAOI, monoamine oxidase inhibitor; Trp/N, nicotinamide given with Trp; N/M, not measured; PC, placebo control; TCAD, tricyclic antidepressant; t.i.d., daily dose given in thirds.

By way of background, humans experience 2 types of sleep: rapid eye-movement (REM) and non-REM sleep. REM sleep occupies ~20–25% of nightly sleep time and is that stage of sleep most commonly associated with dreaming. Non-REM sleep occupies 75–80% of total sleep time and is commonly associated with "deep" sleep, because participants are difficult to arouse (42). At bedtime, the time it takes to fall asleep after lights out is termed the sleep latency (SL) and normally is <15 min (43). An episode of non-REM sleep occurs first, lasting ~90 min, and proceeds through 4 stages from a light form (stage 1) to a deep stage of non-REM sleep [stage 4, also known as slow-wave sleep (SWS)]. This non-REM period is followed by a short REM sleep period. As the night proceeds, this cycle repeats every 90–120 min, with the proportion of REM sleep gradually increasing and the depth of non-REM sleep decreasing (i.e., less time spent in stages 3 and 4) in each succeeding cycle until awakening in the morning.

Many studies examining the effects of Trp in humans appeared over a 20-y period, beginning in the 1960s. Some of these are described in **Table 2.** Trp generally improved sleep, increasing total sleep time and reducing waking time (44–46). In some cases, Trp was reported to modify specific stages of the sleep cycle (e.g., to increase SWS or reduce REM sleep). In other cases, reductions in SL were noted [though not always (47)], with no changes in SWS or REM time (43,48,49). Single doses (taken at bedtime) ranged from small (1 g) to very large (15 g) and were acutely and chronically administered for periods of up to 2 y (Table 2). In almost all cases, no side effects were noted (Table 2); mild nausea was reported occasionally at the larger doses (48), perhaps the consequence of known gastrointestinal

TABLE 2 Effect of oral Trp on sleep in humans[1]

Participants	Treatment	Effect on plasma Trp	Effects/adverse events	Reference
5 normal F, 18–21 y; 7 insomniacs, 48–68 y	DB, CB design. Normals: 10 nights 7.5 g L-Trp (in milk shake), then 10 nights placebo (n = 3); reverse order (n = 2). Insomniacs: 5–10 d placebo, then 5–10 d L-Trp (7.5 g), then 5–10 d placebo. Trp source not specified.	N/M	Normals: Trp increased TST and SWS, decreased REM time. No change in SL. Participants reported sleepiness after taking Trp; occasional nausea. No mood effects next morning. Insomnics: Trp increased TST. No change in SL, SWS, REM time; reduced awakenings. No other side effects noted. Authors stated 7.5 g just below dose producing nausea and vomiting.	44
13 normal M, 21–26 y (7.5 g Trp); 8 M 21–28 y (12 g Trp)	Ingested 0, 7.5, or 12 g L-Trp in applesauce or chocolate 20 min before bed (2100 h). Trp source not specified. Blinding not specified.	N/M	7.5 g: Trp increased SWS, decreased intermittent waking. No change in SL, REM. Extreme drowsiness soon after taking Trp. 12 g: Trp increased REM time, reduced SL. Drowsiness soon after taking Trp. No adverse effects mentioned.	45
10 normal M, 21–26 y, long SL	Oral L-Trp (0, 1, 2, 3, 4, 5, 10, 15 g) 20 min before bed in milkshake. EEG + EOG recorded. Trp source not specified. Blinding not specified.	N/M	L-Trp reduced SL at all doses vs. placebo. Slight decreased waking, no change in SWS (except increased at 10 g). REM time unaffected (except reduced at 10, 15 g). ``Incidence of side effects (feelings of tiredness or grogginess in the morning) no higher on L-Trp nights than on placebo nights.´´	43
Review	Review of his clinical studies to 1977. Used doses up to 15 g at bedtime.	N/M	Trp reduced SL. ``Reports of side effects were extremely rare. In a few instances there were reports of mild nausea at bedtime at doses of 5–15 grams.´´	48
18 F, long SL	DB. Placebo and L-Trp (1,3 g) as tablets 20 min before bedtime. Trp source not specified.	N/M	3 g Trp reduced SL, increased stage 2 NREM during first 3 h of night. No report on side effects.	49
7 F, 5 M, long SL, 35–65 y	DB. CB. Placebo or 1 g L-Trp (pills) at bedtime. Trp source not specified.	N/M	Trp did not shorten SL. No report on side effects.	47
5 M and 3 F, insomniacs, 32–47 y	DB. 4 nights placebo, 3 nights 2 g L-Trp (pills) 30 min before bedtime. Trp source not specified.	N/M	Improved sleep (reduced SL, increased TST and non-REM). ``No side effects were seen.´´	46
16 M and 24 F insomniacs, middle aged	4 nights placebo, 3 nights 2 g L-Trp (pills) 30 min before bedtime, repeat weekly for mean duration 4.3 mo; some followed-up to 2 y who used Trp as needed. Trp source not specified.	N/M	Substantial reduction in insomnia for most participants. Only 2 participants reported ``side-effects´´: increased dreaming with occasional anxiety-provoking dreams in one case, and bloating in the other. ``No major side effects occurred.´´ Positive outcomes in 60% at 3 mo, 80% at end of treatment period.	52, 53
Review			Generally, side effects minimal in all studies discussed: ``The lack of side effects, even with high doses, in administration over long periods of time, or in especially sensitive groups, is of great practical value.´´	54

[1] CB, counterbalanced; DB, double blind; EEG, electroencephalogram; EOG, electrooculogram; N/M, not measured; REM, rapid eye movement sleep; SL, sleep latency; SWS, slow wave sleep; TST, total sleep time.

actions of Trp (50,51). In one chronic study of 40 insomniacs given 2 g L-Trp at bedtime 3 times/wk for 4 mo or longer, only 2 individuals reported side effects of note to the investigators: one participant reported an increasing frequency of dreams, occasionally anxiety provoking and the other experienced bloating (52,53). One of the investigators later summarized: "The lack of side effects, even with high doses, in administration over long periods of time, or in especially sensitive groups, is of great practical value" (54). Similar to the mood studies, Trp source was not specified in sleep studies and thus chemical purity is unknown.

In sleep studies, Trp is taken shortly before bedtime. The occurrence of drowsiness and sleepiness is viewed as a desirable action of the amino acid, not a side effect. Hence, excluding drowsiness as a side effect, the only side effect noted (occasional, mild nausea) was said to occur only at higher doses: e.g., Wyatt et al. (44) noted that 7.5 g Trp is just below the dose at which nausea and vomiting occurs and Hartmann (48) noted mild nausea at doses of 5–15 g. In sleep studies, plasma was not collected and thus plasma Trp excursions are unknown.

Parenthetically, the effects of Trp on sleep may involve not only 5HT but also another biosynthetic product of this amino acid, melatonin. Over the past 50 y, melatonin has been most associated with the pineal gland. Pinealocytes synthesize 5HT using the same pathway as neurons, but then perform 2 additional enzymatic steps on 5HT, N-acetylation and O-methylation, converting it to melatonin (N-acetyl-5-methoxytryptamine). Pineal-derived melatonin has probably been most studied for its role in reproduction (55). Over the past 2 decades, however, melatonin has been found to be synthesized in and released by a variety of nonpineal cells and to have many nonreproductive actions (56). Moreover, whereas melatonin production does not appear to be stimulated by Trp (though 5HT synthesis is) in pinealocytes (57), it is stimulated in nonpineal, melatonin-producing cells, such as those in the gut, and leads to increases in plasma melatonin concentrations (58). Melatonin is a fat-soluble hormone and thus readily penetrates the brain from the blood. And one nonreproductive effect of melatonin is to reduce SL and improve sleep in insomniacs (59). Hence, the effects of Trp on sleep may be mediated not just by neuronal 5HT but also by melatonin produced by cells far removed from the brain.

Normal individuals

Whereas the reported action of Trp to improve sleep can be viewed as a desirable effect in sleep studies, it may also be viewed as a side effect in other contexts. As indicated in **Table 3**, a number of studies in normal participants have viewed such effects as side effects. Smith and Prockop (38) tested a range of Trp doses (0, 30, 50, 70, and 90 mg/kg) in a single-administration paradigm in the morning, with participants receiving each dose on separate occasions. The authors viewed such effects as drowsiness, listlessness, and falling asleep, which occurred even at the 30-mg/kg dose, as adverse. Such effects were common in later studies, where single oral doses were administered in the same dose range (60–63). Trp has also been given i.v. over 30–180 min at doses up to 10 g, with drowsiness and light-headedness being commonly reported effects (61,64–67).

In several of these studies, plasma Trp concentrations were measured and a variety of doses examined. With the obvious limitations in mind, it is of interest to explore whether there might be a rough correlation among Trp dose, the elicited increase in plasma Trp, and reported side effect incidence (because the rise in plasma Trp would raise brain Trp levels and 5HT synthesis, leading to side effects caused by 5HT or perhaps some other direct or indirect action of Trp in brain). Hence, proceeding from lowest to highest Trp dose (Table 3) and assuming a body weight of 70 kg (body weights were almost never specified), an oral dose of 15 mg/kg L-Trp raised plasma Trp ~2.5-fold and produced no side effects (68). An oral dose of 30 mg/kg elevated plasma Trp ~3-fold and caused fatigue (63). However, an oral dose of 32 mg/kg, which caused a 5-fold rise in plasma Trp, produced "remarkably few side effects" and no psychic or mental changes (69). Fifty mg/kg L-Trp produced an 8-fold rise in plasma Trp and drowsiness and lethargy reported to be annoying (62). A dose of 70 mg/kg (70 kg body weight assumed) caused an 8-fold rise in plasma Trp and was associated with drowsiness, clumsiness, mental slowness, and nausea (60). An i.v. dose of 75 mg/kg L-Trp raised plasma Trp 5-fold; participants reported feeling drowsy, clumsy, and lethargic, and 100 mg/kg raised plasma Trp 8-fold and produced the same side effects (64). At 100 mg/kg L-Trp, Yuwiler et al. (62) reported an 11-fold rise in plasma Trp, drowsiness, lethargy, weakness, faintness, and mild nausea. An i.v. dose of 130–140 mg/kg L-Trp has also been studied, with no measurements of plasma Trp. In one study, the treatment was well tolerated by participants, with the occasional appearance of light-headedness (66); in another study, side effects of mental sedation, sleepiness, light-headedness, and occasional nausea were reported (67). Finally, in chronic studies of L-Trp, in which the amino acid was administered at 40–50 mg/(kg · d) (1 g 3 times/d) for 6 (68) or 12–14 d (70), plasma Trp rose ~2.5-fold after a 1-g dose (68) and the occurrence of side effects was not significant (68,70). In a chronic study by Yuwiler (62), in which 50 mg/(kg · d) L-Trp was administered as a single daily dose, producing an ~7-fold rise in plasma Trp, lethargy was reported.

Taking these studies together, while recognizing that some involved relatively few participants, designs differed, and in some cases body weights were not provided, it would appear that a single, oral L-Trp dose somewhere between 30 and 50 mg/kg, which causes at least a 5-fold rise in plasma Trp, may begin to elicit drowsiness and sleepiness [though Hartmann (48) reported that doses as low as 1 g could reduce SL at bedtime]. Doses >50 mg/kg may begin to elicit some occasional feelings of nausea and may depend on the manner in which Trp has been administered [i.e., in pill form (60) or incorporated into a vehicle, such as a milk shake (62)].

Trp and the EMS

In late 1989, a serious medical condition appeared suddenly in the U.S. population and was designated EMS based on the key symptomology of debilitating myalgia and high eosinophil counts in peripheral blood (71). A common feature of almost all individuals presenting with EMS was the use of supplemental Trp, typically for insomnia and mood elevation (10,72). Within a few weeks of the first reports, the U.S. FDA banned the sale of products containing Trp manufactured outside the United States. The incidence of EMS declined rapidly thereafter, although between November 1989 and February 1990, some 1500 cases were reported nationally to the U.S. CDC (9). Given that Trp had been used in the population for decades with minimal reports of EMS-like symptoms and the subsequent finding that the Trp used by individuals who developed EMS derived from specific batches of Trp produced by a single manufacturer around the time that EMS emerged, the strong suspicion developed that a contaminant, rather than the Trp, was responsible (9,11,72). This view was strengthened by the fact that although Trp was withdrawn from general use in the United States in 1989, it remained available for medical purposes, supplied by other manufacturers, and no further EMS cases developed (73).

TABLE 3 Effects of oral and i.v. L-Trp in normal humans[1]

Participants	Treatment	Effect on plasma Trp	Effects/adverse events	Reference
2 F, 5 M, normal, 21–41 y	ON fast, L-Trp (Nutritional Biochemicals; in applesauce, 0, 30, 50, 70, 90 mg/kg). Participants received all doses. Neurologic exams for 8 h not blinded.	N/M	5/7 drowsy, 30 mg/kg Trp; 7/7 listless, 90 mg/kg. Fell asleep. Euphoria. Nystagmus at 90 mg/kg, viewed by authors as adverse effects. EEG normal when awake.	38
4 normal F, 4 normal M, 18–40 y	ON fast. L-Trp (4, 5, 10 g) or L-Trp (10 g) (Sigma) i.v. in morning, up to 150 mL solution over 20 min. Blood sampled for 60 min. Not blinded.	N/M	10 g L-Trp, not D-Trp, caused large rise in plasma prolactin, 5 g less; 4 g no rise. i.v. Trp (5–10 g) well tolerated; occasional light-headedness, flushing, and slight pain at the infusion site.	66
6 normal M	ON fast; DB. Infuse L-Trp i.v. (saline, 75, 100 mg/kg in 1 L saline) over 3 h. Trp source not specified.	Baseline 100 nmol/mL; 75 mg/kg peak, 500 nmol/mL; 100 mg/kg peak, 800 nmol/mL at 3 h.	Drowsy, clumsy, bored, incompetent, dreamy, mentally slow, lethargic on both doses.	64
27 schizophrenic M, 24 prison M, 5 normal M	ON fast, ingest 32 mg/kg L-Trp (General Biochemicals) in apple sauce. Fasting and post-Trp blood samples. Not blinded.	Fasting 75 nmol/mL; peak 250–450 nmol/mL at 1 h.	Remarkably few side effects; no psychic or mental changes.	69
Healthy M (6) and F (4), 21–38 y	DB, CB design. Time of day, prandial state not specified. Placebo or 5 g L-Trp orally (Cambrian Chemicals), study ran 3 h.	Baseline 65 nmol/mL rose to 510 nmol/mL 2 h after Trp.	Headache reported, peaking 1–2 h after Trp. Trp produced more drowsiness, clumsiness, mental slowness than placebo. Nausea, possibly linked to pill bitterness.	60
5 normal M 20–50 y	ON fast; not blind. Vehicle (180 mL chocolate drink); acute L-Trp, 50 or 100 mg/kg; chronic L-Trp, 50 mg/kg·d^{-1} × 14 d (all in vehicle). Trp source not specified.	Baseline 75 nmol/mL; 50 mg/kg peak, 600 nmol/mL; 100 mg/kg peak, 830 nmol/mL; peak after d 9 dose, 500 nmol/mL.	Short-term drowsiness/lethargy ``annoying.'' At 100 mg/kg, 2 participants reported weakness, faintness, mild nausea.	62
6 normal F, 4 normal M, 27–57 y	DB, CB design. ON fast; infused i.v. 0.45% saline with or without L-Trp (~100 mg/kg, Sigma) over 20 min; sampled blood for 3 h.	N/M	Plasma prolactin and growth hormone rose significantly. Trp well tolerated. Occasional mild, transient nausea. Drowsiness, mellowness, highness at 30–60 min.	65
Normal M (6) 22–45 y	DB, CB design. L-Trp (Sigma) 1 g t.i.d. (3 g/d) with meals for 6 d, placebo for 6 d.	At t = 90 min, placebo 51 nmol/mL, Trp (1 g) 130 nmol/mL.	``None of the volunteers experienced any adverse event or drowsiness during the study period.''	68
11 Normal M, 22–31 y	ON fast, L-Trp (0, 5, 7.5, 10 g in saline; source not specified) infused i.v. over 30 min. All participants got all Rx. Not blinded. Sampled blood 210 min.	N/M	Plasma growth hormone, prolactin rose to peak at 30–60 min. Trp impairments on performance tests dose related. All doses increased mental sedation. Sleepiness and lightheadedness reported; all effects transient. Occasional report of nausea.	67
Healthy M (4) and F (2), 24–35 y	ON fast, SB. Test before and for 4 h for fatigue after caffeine-free diet Coke with L-Trp (30 mg/kg; SHS, Liverpool, UK) or nothing. Participants got both treatments.	Baseline 68 nmol/mL; 30 mg/kg peak, 219 nmol/mL.	Subjective fatigue rose by 3 h on L-Trp. Objective measure of central fatigue increased by L-Trp vs. placebo. Muscle function unaffected or improved.	63
Normal M (50) and F (48), 18–67 y	DB, CB design. L-Trp 1 g t.i.d. (3 g/d) or placebo with meals (Tryptan ICN Canada) for 12 d, then treatment switched.	N/M	``Very few side effects were reported.'' Trp and placebo side effects not statistically different (fatigue, upset stomach, lightheadedness, headache).	70

[1] CB, counterbalanced; DB, double blind; EEG, electroencephalogram; N/M, not measured; ON, overnight; SB, single blind; t.i.d., daily dose given in thirds.

As noted, the most dramatic initial effects of EMS were severe myalgia and high circulating eosinophil counts (in the absence of infection) (71), though the acute syndrome also typically elaborated fatigue, muscle tenderness, muscle cramps, muscle weakness, arthralgia (joint pain), paresthesia (skin sensations; e.g., burning, itching, prickling, tingling), rash, and dyspnea (shortness of breath; labored breathing) (74). But symptoms did not cease following the discontinuation of Trp-containing products. For example, 3–6 mo after Trp was discontinued, patients had developed notable scleroderma-like skin thickening, and the presence of severe myalgia, cramps, and spasms was common (74). These symptoms had not resolved by 16–24 mo. The median daily Trp dose in EMS patients had been ~1500 mg (10th percentile, 500 mg; 90th percentile, 4000 mg) (9), or ~20 mg/(kg · d) for a 70-kg individual.

In this regard, another perspective suggesting that Trp itself did not cause EMS was the marked dissimilarities between EMS symptomology and that of Trp itself (prior and subsequent to the EMS outbreak). As noted, EMS symptoms are marked, painful, focused on muscle, joints ,and skin, and do not usually resolve when use of the product ceases. In contrast, symptoms and side effects commonly reported for Trp are drowsiness, sleepiness, dizziness, and occasionally muscle twitching/tremor (see above). Even when Trp is combined with potent 5HT drugs and together occasionally induce the 5HT syndrome, typical symptoms are agitation, delirium, coma, mydriasis, sweating, tremor, and myoclonus (36,37). And, these symptoms rapidly dissipate when Trp is discontinued [e.g., (25,62,67)].

Summary

Trp is the precursor of the neurotransmitter 5HT. 5HT synthesis in neurons varies directly with Trp supply to brain. Ingesting Trp raises brain Trp levels and stimulates 5HT synthesis and release, leading to functional effects, such as improving mood and sleep. For this reason, supplemental Trp is taken by humans to elevate mood and improve sleep. Trp has been studied for these actions for 5 decades now and surprisingly few side effects have been noted or reported. Where reported, side effects have generally been mild, even at substantial acute doses of the amino acid. Hence, Trp does not appear to possess significant toxicity in the context in which it has been used and studied in humans. One caveat is that with the increasing use of 5HT drugs (agents that enhance 5HT function) in society, most notably 5HT reuptake inhibitors [e.g., fluoxetine (Prozac), citalopram (Celexa), fluvoxamine (Luvox), sertraline (Zoloft), and escitalopram (Lexapro)], the use of one or more of such agents, in combination with Trp, can occasionally elicit a serious condition termed the "5HT syndrome," which requires intervention. The appearance in late 1989 of EMS, a medically serious and occasionally fatal condition associated with supplemental Trp use, is not thought to be related to the Trp but rather to contaminants introduced during manufacturing. Consistent with this view, the symptoms of EMS do not overlap with side effects associated with Trp use over many decades. The key conclusion is that, as for almost all nutrients, the available published literature used to probe for side effects of Trp is limited, never focused on assessing side effects as a principal goal, and remarkably underpowered statistically. These facts make it impossible to identify with any precision the Trp dose at which effects first emerge, much less the dose at which significant side effects begin to occur. As such, the analysis offered in this review in relation to dose is at best speculative. A properly designed and powered study is needed before any realistic consideration can be given regarding upper limits for Trp use.

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