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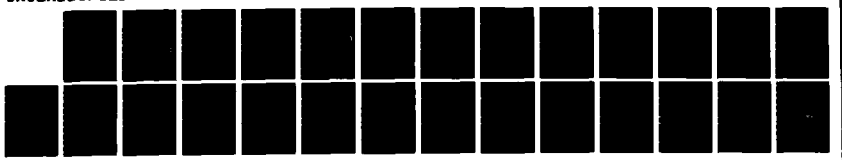

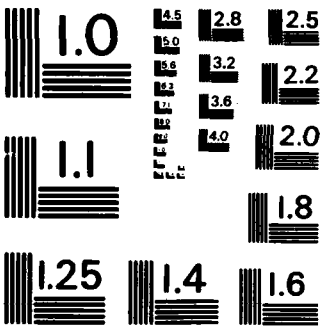

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PLASMA L-TRYPTOPHAN LEVELS, SUBJECTIVE SLEEPINESS AND DAYTIME SLEEP

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(U) The amino acid, l-tryptophan, is the direct dietary precursor of brain serotonin. The inconsistent effects of l-tryptophan on nighttime sleep are reviewed. Effects on daytime nap sleep are presented. L-tryptophan (4 grams) significantly reduces daytime sleep latency in morning and afternoon naps, without alteration of sleep stages. The waking EEG shows significantly more alpha and theta following l-tryptophan administration. These findings are consistent with other

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20. ABSTRACT (continued)

daytime studies showing significant elevations in subjective sleepiness on the Stanford Sleepiness Scale following l-tryptophan. L-tryptophan is described as a mild and physiological hypnotic which is effective when administered in environments conducive to sleep.

NAVAL HEALTH RESEARCH CENTER REPORT #80-25

Plasma L-tryptophan Levels, Subjective Sleepiness, and Daytime Sleep

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Plasma L-tryptophan Levels, Subjective Sleepiness, and Daytime Sleep

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Introduction

Interest in l-tryptophan as a hypnotic stems from its metabolic role as the direct dietary precursor of the neurotransmitter serotonin and from neurochemical studies suggesting that an important function of brain serotonin is the physiological control of sleep. Work by Jouvet (Jouvet and Renault, 1966; Jouvet, 1968, 1972) has demonstrated significant correlations between the extent of median raphe damage, decreases in brain serotonin levels, and decreases in total sleep time in cats. The more commonly used sedative/hypnotics have been determined to have undesirable effects associated with their use. Rapid development of tolerance and the presence of withdrawal effects are problems in the use of barbiturate-hypnotics (Oswald and Priest, 1965; Kales et al, 1968, 1974). Morning performance decrements and substantial alteration of sleep EEGs have been demonstrated in benzodiazepine use (Church and Johnson, 1979; Johnson et al, 1979). Sleep researchers have had a strong motivation to direct their work toward identification of a safe but effective sleeping pill. L-tryptophan has been termed a "natural" (Wyatt et al, 1970; Hartmann et al, 1971) or "physiological" sedative (Cooper, 1979), but the putative central mode of action of l-tryptophan remains unestablished and inconsistencies in results of various sleep studies are as yet unexplained.

Plasma L-tryptophan and Brain Serotonin

Metabolic studies indicate that serotonin levels in the brain are determined by the availability of tryptophan in plasma. The plasma level of tryptophan is rapidly altered by ingestion of dietary protein or by administration of l-tryptophan (Moir and Eccleston, 1968; Young et al, 1969; Fernstrom and Jacoby, 1975; Wurtmann and Fernstrom, 1976). Administration of l-tryptophan has been shown to be effective in elevating serotonin levels in sites at which serotonin naturally occurs in rat brain (Moir and Eccleston, 1968). Specifically, these increases occur in serotonergic neurons which contain the required enzyme for conversion of l-tryptophan to 5-OH-tryptophan. (Administration of 5-OH-tryptophan, on the other hand, produces widespread increases in serotonin levels due to the ubiquitous presence of the decarboxylase enzyme in brain tissue.)

L-tryptophan circulates in plasma in both the free form and bound to serum albumin (McNenamy and Oncley, 1958). It has been demonstrated in experimental animals that the hydroxylase enzyme at the first step in the serotonin synthetic pathway is not saturated (Friedman et al, 1972). The availability of the amino acid precursor is believed to be the rate-limiting factor in serotonin synthesis. Some researchers have presented evidence that it is the level of free (non-albumin bound) plasma tryptophan, rather than total blood tryptophan levels, which correlates most closely with central 5HT levels (Tagliamonte et al, 1973; Gessa and Tagliamonte, 1974; Curzon and Knott, 1974; Young et al, 1976). Other researchers present data supporting the concept that it is the ratio of total plasma tryptophan to the concentration of competitor amino acids

which regulates brain serotonin synthesis (Fernstrom and Wurtman, 1972). It has been suggested that this ratio may be further refined to include the level of plasma free tryptophan in the numerator, since this portion of plasma tryptophan appears to be the pool which can compete directly with other neutral amino acids for up-take into the brain (Morgan et al, 1975).

While it is clear that physiological mechanisms are available whereby dietary l-tryptophan can have direct effects on the level of brain serotonin, other aspects of the serotonergic-sleep model have been questioned. The basic concept of the critical role of serotonin in sleep induction and maintenance based on Jouvet's work (1966, 1968, 1972) has become more controversial; Dement et al (1972) found that sleep occurred in cats after chronic blocking of serotonin formation and Rechtschaffen et al (1973) found no consistent sleep changes in rats after parachlorophenylalanine (PCPA). Wyatt's work (Wyatt et al, 1970) showing l-tryptophan effects on sleep in subjects pretreated with PCPA suggested that effects on REM and SWS may be mediated by non-serotonergic mechanisms. However, this interpretation can be questioned, based on more recent work in cats which demonstrates that l-tryptophan (150 mg/kg) restores brain serotonin and reverses the effects of PCPA pretreatment (Marsden and Curzon, 1975). Other research indicates that the sedative effects of l-tryptophan are not mediated by the conversion to tyramine (Hodge et al, 1964), although it has been suggested in a preliminary report that the nicotinamide pathway may be involved (Pegram et al, 1975). Recent research on rat sleep with l-tryptophan and 2-amino-3-(1-naphthyl) propanoic acid, a tryptophan analogue, suggests that hypnotic effects may

proceed via attenuation of activity in catecholaminergic pathways (Fornal et al, 1979; Wojcik et al, 1979).

A consideration of the inconsistencies of the reported effects on human sleep and recent animal neurophysiological work suggests that the hypnotic effects of l-tryptophan may proceed via a serotonergic modulation of the waking state, rather than by a triggering of sleep onset mechanisms. Studies on serotonin precursors given to cats have been demonstrated to produce deactivation of the waking EEG, with no alteration of sleep parameters (Ursin, 1976). Research on unit activity in cats has suggested that serotonergic neurons are involved in the modulation of activation levels (Trulson and Jacobs, 1979).

L-tryptophan and Nocturnal Sleep

Levels of free plasma tryptophan show a circadian variation with midnight values significantly elevated (by 45%) over noontime values (Tagliamonte et al, 1974; Wirz-Justice et al, 1975). These increases in level at the usual bedtime support the speculation that plasma tryptophan levels may be the natural regulator of sleep onset (Hartmann et al, 1971). In a recent review, Cooper (1979) summarizes sleep study findings by stating that l-tryptophan appears to have hypnotic effects when administered at bedtime but speculates that "sleep occurs naturally only when the plasma and brain l-tryptophan (and 5-HT) levels exceed a certain critical value, and that the administration of l-tryptophan, at least in modest doses, can trigger sleep mechanisms only at night" (p. 101). The metabolism of l-tryptophan is regulated by many control systems and proceeds via several alternative pathways (Knox, 1966; Knox et al, 1966; Azmitia and McEwen, 1969; Hardeland, 1969; Fernstrom and Wurtman, 1972;

Tagliamonte et al, 1973; Curzon and Knott, 1974; Gessa and Tagliamonte, 1974). Such factors as time of administration, dose levels, and the times post-drug when dependent variables are measured are factors which may influence experimental findings.

Evaluation of the hypnotic efficacy of l-tryptophan has been the goal of a substantial number of sleep studies. Some investigators report that l-tryptophan administered prior to bedtime significantly reduces nighttime sleep latency (Hartmann, 1967; Williams et al, 1969; Hartmann et al, 1970; Griffiths et al, 1972; Hartmann et al, 1974; Hartmann and Elion, 1977; Brown et al, 1979; Spinweber and Hartmann, 1979), while other groups do not report sleep-facilitating effects (Wyatt et al, 1970; Brezinova et al, 1972; Nicholson and Stone, 1979; Small et al, 1979; Adam and Oswald, 1979). Claims that l-tryptophan does not alter sleep stages as do the commonly used barbiturate and benzodiazepine hypnotics are supported by studies on small doses (1-5 grams) (Hartmann et al, 1974; Spinweber and Hartmann, 1978), although larger doses have been demonstrated to alter sleep stage parameters. While the reported direction of these stage alterations are conflicting for REM latency (Oswald et al, 1966; Wyatt et al, 1970) and REM time (Williams et al, 1969; Wyatt et al, 1970; Griffiths et al, 1972), the reports of effects of the larger doses on delta sleep (Stages 3 and 4) are consistent in demonstrating increases (Williams et al, 1969; Wyatt et al, 1970; Griffiths et al, 1972; Hartmann et al, 1974). The delta-sleep enhancing effect is further suggested by a review of data from a number of the smaller dose studies by Hartmann and colleagues which indicates a general trend toward increased Stages 3 and 4, although this effect in

the individual studies does not reach significance (Spinweber and Hartmann, 1978; Hartmann and Spinweber, 1979).

Daytime and Evening Administration

A study recently completed at the Naval Health Research Center, San Diego, demonstrates hypnotic effects in daytime naps scheduled at 0950 and 1350, each begun one hour after l-tryptophan administration (Spinweber et al, 1980). Twenty subjects each participated in two daytime recording sessions after l-tryptophan (4 grams) or a matching placebo, assigned in a counterbalanced order on a double-blind basis. The medications were administered at 0850 to a morning group and at 1250 to an afternoon group (Table 1). Subjective measures were taken prior to drug (baseline), at 25 minutes post-drug, and following a 2-hour nap. The nap began 1 hour post-drug and was both preceded and followed by a recording of waking EEGs. Blood samples were drawn 30 minutes after drug administration and subsequently analyzed for plasma total and free tryptophan levels.

Table 1 here

L-tryptophan significantly reduced nap sleep latency (time from lights out to the onset of Stage 2) (23.4 minutes vs. 12.6 minutes; T (Wilcoxon Matched Pairs Signed Ranks Test) = 49, $p < .05$, two-tailed). There was no differential effect of time of day of administration (morning vs. afternoon groups) on the reduction of sleep latency. Nap sleep stage variables did not differ between the two conditions (Table 2). Administration of l-tryptophan significantly elevated plasma total tryptophan ($t_{(19)} = 6.11$, $p < .001$) and free tryptophan levels ($t_{(19)} = 5.72$, $p < .001$). Analysis of waking EEGs revealed a significant increase in alpha time ($F_{(1,16)} = 5.75$, $p < .05$) and theta time

Table 2 here

($F_{(1,16)} = 6.08$, $p < .05$) and a decrease in alpha frequency ($F_{(1,16)} = 4.56$, $p < .05$) in the l-tryptophan condition. Self-report measures did not reveal any change in reported sleepiness or activation-deactivation at the times when questionnaires were administered.

Other studies using subjective sleepiness as a dependent variable have also demonstrated hypnotic properties of l-tryptophan when administered at various clock times beside the subjects' normal bedtimes. One study addressed the relationship between l-tryptophan administration and subjective sleepiness at the time of the noon meal (Hartmann et al, 1979). Subjects ate a standard laboratory lunch consisting of 10 grams of casein acid hydrolysate dissolved in 200 ml of beef bouillon to which various doses of l-tryptophan (0, 1/4, 1/2, 1, 4 grams) were added in balanced order on a double-blind basis. Subjects completed the Stanford Sleepiness Scale (SSS) every 15 minutes and the Profile of Mood States (POMS) one hour after the meal.

The meal containing l-tryptophan (4 grams) produced a marked and significant increase in sleepiness on the SSS beginning 30 minutes after the meal and continuing for 2 hours. One gram had smaller effects in the same direction. On the POMS, there was a dose-dependent decrease in "vigor" with increasing dietary l-tryptophan. Analysis of plasma for total tryptophan levels demonstrated a significant dose-dependent increase for all dose levels; plasma free tryptophan was significantly increased by the l-gram and 4-gram doses. Related findings have also been reported in a study of carbohydrate and protein diets. Reported sleepiness on the SSS was significantly higher 120 minutes after consumption of the carbohydrate meal than after the protein meal

(Spinweber, 1977). Based on metabolic studies in rats (Fernstrom and Jacoby, 1975), the carbohydrate meal is hypothesized to potentiate the entrance of plasma l-tryptophan into brain, while the protein meal, containing competing amino acids, may reduce the availability of l-tryptophan to brain.

The subjective effects of early evening administration of powdered amino acids have been studied in twelve normal male and female subjects (age 18-30) who took 4 grams of l-tryptophan, l-leucine, or placebo, approximately 2-3 hours prior to bedtime: Subjects rated their subjective sleepiness on the 7-point SSS at the time of drug administration and continued the self-rating at 15-minute intervals for 3 hours or until they went to bed.

Data were analyzed using an Analysis of Variance for repeated measures. There were no significant differences between the three conditions 15 and 30 minutes after ingestion (Figure 1). However, at 45, 60, 75, and 90 minutes after ingestion, the main effect of treatment conditions revealed significant F's ranging from $p < .004$ to $p < .014$. Post-hoc pairwise comparisons demonstrated that subjective sleepiness on l-tryptophan was significantly greater than that reported on placebo ($p < .05$) for the 45-90 minute period. At no time point were measures of reported sleepiness on l-leucine significantly different from placebo (Hartmann et al, 1976).

Figure 1 here

Summary and Discussion

The plasma data presented above indicate that oral administration of l-tryptophan (4 grams) produces major elevations in plasma tryptophan parameters as early as 30 minutes after administration (Spinweber et al,

1980). However, levels of subjective sleepiness are not increased as early as 25 minutes post-ingestion nor as late as 3 hours 10 minutes post-ingestion (Spinweber et al, 1980), but are elevated at 30-45 minutes after ingestion (Hartmann et al, 1976, 1979). Presumably, in a serotonergic model, the later appearance of subjective effects is due to the additional time required for transport of l-tryptophan across the blood-brain barrier and potentiation of the serotonergic metabolic pathway. These temporal factors shed some light on the negative findings reported by Nicholson and Stone (1979). In the daytime portion of their study, l-tryptophan (4 grams) or placebo were administered at 1400, and this time point was also chosen as "lights out" for measurement of sleep latencies. In the placebo condition, the mean latency from lights out to Stage 2 was 22.2 minutes, and, on l-tryptophan (4 grams), was 21.8 minutes. It is suggested that the subjects in the Nicholson and Stone study fell asleep too quickly after lights out to permit a significant elevation of plasma tryptophan levels and onset of subjective sleepiness which are prerequisite for l-tryptophan to have a sleep-facilitating effect.

Based on findings that l-tryptophan increases alpha and theta activity in the waking EEG and reduces sleep latency without alteration of sleep parameters (Spinweber et al, 1980), the most parsimonious explanation for the hypnotic effect is that l-tryptophan potentiates a serotonergically mediated deactivation of the waking state which facilitates more rapid sleep onset (Ursin et al, 1980). It is suspected that this physiological deactivation may be readily reversible in situations inconducive to sleep, thus accounting for Broadhurst's report

(1977) that daytime administration of l-tryptophan does not produce slowing of reaction times as do barbiturate hypnotics, although a limitation on this interpretation is that the small dosage (2 grams) used by Broadhurst has not been experimentally demonstrated to have daytime hypnotic effects. The physiological nature of the deactivation and its proposed reversibility suggests that l-tryptophan's hypnotic efficacy may be highly influenced by the baseline arousal state of subjects and the nature of the environment and experimental protocol employed. Therein may lie l-tryptophan's fundamental strength and weakness as a hypnotic. On the positive side of the coin, use of l-tryptophan may not be associated with performance decrement and post-nap hangover, common to other sedative hypnotics. However, as is suggested by inconsistencies in previously cited studies on sleep latency in nighttime sleep, its hypnotic effects may be variable across individuals and groups studied.

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Table 1

Daytime L-tryptophan Study Protocol

Schedule Morning Group	Procedure	Schedule Afternoon Group
0830	Subject arrives: Hook-up begins	1230
0845-0849	Baseline SSS and Thayer	1245-1249
0850	Drug administration (L-tryptophan, 4 grams, or placebo)	1250
0915-0919	Post-drug SSS and Thayer	1315-1319
0920	Blood sample drawn	1320
0930-0940	Waking EEG, eyes open	1330-1340
0940-0950	Waking EEG, eyes closed	1340-1350
0950-1150	Nap	1350-1550
1150-1155	Waking EEG, eyes open	1550-1555
1155-1200	Waking EEG, eyes closed	1555-1600
1200-1204	Post-nap SSS and Thayer Post-nap questionnaire	1600-1604
1205	Session completed: Remove electrodes	1605

Table 2

Daytime L-tryptophan Study

Sleep Variable	Placebo $\bar{X}$ (± SD) (min)	L-tryptophan $\bar{X}$ (± SD) (min)
Sleep Latency		
(time from lights out to Stage 2 onset)	23.40 (23.90)	12.60 (9.80)*
Total Bed Time	119.80 (0.34)	119.80 (0.38)
Total Sleep (Stages 2, 3, 4, REM)	66.78 (26.99)	74.95 (31.08)
Stage 1	14.05 (9.62)	16.38 (7.78)
Stage 2	43.35 (16.53)	53.75 (19.76)
Stage 3	9.57 (8.57)	6.30 (7.38)
Stage 4	4.70 (8.25)	4.63 (8.36)
Delta Sleep (Stages 3 + 4)	14.27 (12.20)	10.92 (13.69)
REM	9.15 (12.00)	10.27 (11.20)
Total Stage Wake	38.65 (28.52)	27.95 (29.14)

*$p < .05$, Wilcoxon Matched Pairs Signed Ranks Test

Legend for Figure 1:

L-tryptophan (4 grams) produced a significantly greater increase in subjective sleepiness than placebo on the Stanford Sleepiness Scale (SSS) at 45-90 minutes post-ingestion. L-leucine (4 grams) did not produce significant increases in subjective sleepiness in comparison with the placebo.

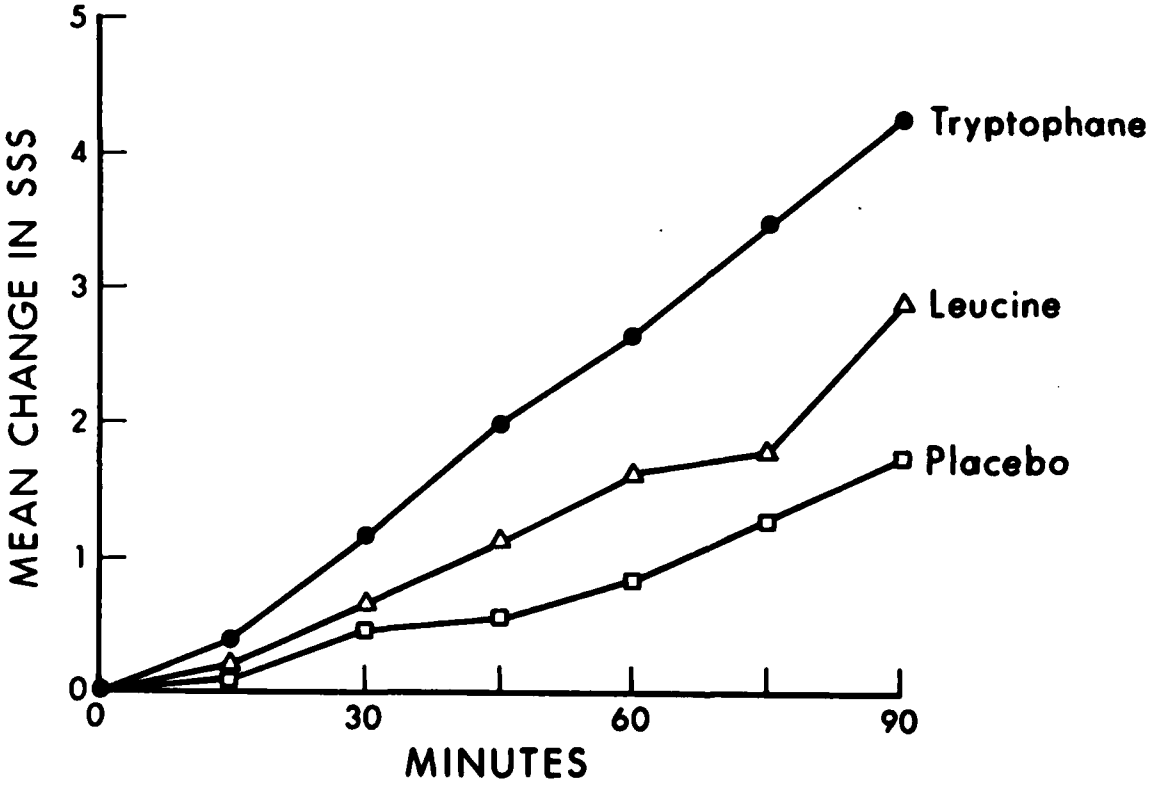
MEAN CHANGE IN SSS
5
4
3
2
1
0
0
30
60
90
MINUTES
Tryptophane
Leucine
Placebo

Figure 1

END

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