Psychopharmacology (1986) 88:213–219

Psychopharmacology

Hormonal and behavioral effects associated with intravenous L-tryptophan administration

Andrew Winokur[1,2], **Nicholas D. Lindberg**[1], **Irwin Lucki**[1], **Jennifer Phillips**[1], **and Jay D. Amsterdam**[1]
From the Department of Psychiatry[1] and Pharmacology[2], University of Pennsylvania, USA

Abstract. Doses of 5.0, 7.5 and 10.0 g L-tryptophan, the amino acid precursor of serotonin, or saline alone were administered by IV infusion to a group of 11 healthy male subjects, and both hormonal and behavioral responses were monitored. Significant increases were observed in plasma concentrations of growth hormone and prolactin after all three doses of L-tryptophan, but not after saline infusion. No alterations in cortisol or thryotropin were noted at any level. Examination of behavioral effects of L-tryptophan revealed a dose-dependent impairment in performance on the symbol copying test. In addition, L-tryptophan produced significant effects on mental and physical sedation, but did not alter subjective ratings of tranquilization. In agreement with some prior reports, these observations support the ability of L-tryptophan, when administered IV in high doses, to produce pronounced effects on the central nervous system in humans, and suggest the potential utility of this paradigm as a neuroendocrine challenge test.

Key words: L-Tryptophan – Growth hormone – Prolactin – Behavioral effects

Current concepts of the biochemical bases of affective disorders have been focused to a considerable extent on alterations in central monoaminergic systems. Earlier pharmacological studies of the mechanism of action of the tricyclic antidepressant drugs and monoamine oxidase inhibitors suggested that these compounds produce their therapeutic effects by enhancing transmission in norepinephrine (Schildkraut 1965; Bunney et al. 1965) or serotonin (Coppen 1967; Lapin and Oxenkrug 1969; van Praag 1974) pathways. More recent studies employing chronic administration of antidepressant compounds have suggested that monoaminergic systems undergo compensatory alterations in response to presynaptic blockade of neurotransmitter uptake. These compensatory changes have been shown to occur both presynaptically (e.g., decreased tyrosine hydroxylase activity in noradrenergic neurons) (Segal et al. 1974) and postsynaptically (e.g., decreased receptor number following chronic treatment with antidepressant compounds) (Bergstrom and Kellar 1979; Savage et al. 1980; Peroutka and Snyder 1980). Clarification of the relevance of these neurochemical mechanisms to the clinical course of drug therapy will depend upon the development of reliable measures of brain monoaminergic function in humans.

Clinical studies of serotonergic activity in depression have involved measurement of concentrations of serotonin, its precursor tryptophan and its metabolite 5-hydroxyindoleacetic acid in spinal fluid, plasma, urine and brain tissue obtained at autopsy (Ashcroft et al. 1966; van Praag et al. 1970; Coppen et al. 1973; Strom-Olsen and Weil-Malherbe 1958; Pare and Sandler 1959). All such measures, however, share the same limitations, i.e., they do not directly reflect serotonin activity in the central nervous system (CNS). The development of reliable methods to assess the functional activity of central serotonergic systems in humans would be of value in clarifying the involvement of this neurotransmitter in affective disorders. Moreover, such methods would provide a means to assess the effects of antidepressant drugs on the responsiveness of CNS serotonergic systems.

A substantial body of data supports a role for serotonin in neuroendocrine regulation (Anton-Tay and Wurtman 1971). For example, tryptophan and 5-hydroxytryptophan (5-HTP), precursors of serotonin biosynthesis, have been administered in clinical studies to stimulate hormone secretion. Some studies have reported increased concentrations of prolactin (PRL), growth hormone (GH), adrenocorticotropin (ACTH) and cortisol after the administration of serotonin precursors (MacIndoe and Turkington 1973; Kato et al. 1974; Lancranjan et al. 1977; Wirz-Justice et al. 1976; Mueller et al. 1974; Woolf and Lee 1976; Fraser et al. 1979; Imura et al. 1973; Modlinger et al. 1980; Meltzer et al. 1984), but these findings have not been consistently replicated (Smythe et al. 1976; Faber et al. 1977; Glass et al. 1980; Handwerger et al. 1975; Westenberg et al. 1982; Lal et al. 1980). Although the majority of the studies cited are well-designed and controlled, variations in experimental conditions make comparison of the results obtained extremely difficult. These conditions include precursor type, dose, route of administration, frequency and duration of blood sampling, hormones evaluated and sex distribution of subjects.

L-Tryptophan is of potential value as a neuroendocrine provocative agent because it is selectively taken up and converted to serotonin in serotonergic neurons. Because tryptophan hydroxylase, the rate-limiting enzyme in the biosynthesis of serotonin, has a low affinity for its substrate, addition of tryptophan through dietary or pharmacological means can lead to increases in brain serotonin concentra-

Offprint requests: A. Winokur, Department of Psychiatry G-1, 918 Gates Pavilion, 3400 Spruce Street, Philadelphia, PA 19104, USA

tion (Fernstrom and Wurtman 1971, 1972). Another widely used serotonin precursor, 5-HTP lacks the specificity of tryptophan for serotonergic neurons, since it can be converted to serotonin in catecholamine neurons by the enzyme L-aromatic amino acid decarboxylase (Fuxe et al. 1971). Plasma free tryptophan concentrations correlate significantly with both lumbar and ventricular cerebrospinal fluid tryptophan (Curzon et al. 1980). Moreover, following IV administration of tryptophan prior to subcaudate tractotomy, a strong correlation was demonstrated between plasma free tryptophan and cerebral cortical tissue tryptophan (Gillman et al. 1980). While there is evidence from preclinical studies that plasma tryptophan correlates with brain serotonin concentration (Fernstrom and Wurtman 1971), this relationship remains to be established in humans.

Administration of tryptophan by IV infusion avoids difficulties with unreliable gastric absorption and variable first-pass hepatic metabolism. Thus, this approach might allow standardization of a procedure which could help to clarify inconsistencies in the literature on tryptophan as a neuroendocrine provocative agent. Recently, Charney et al. (1982) and Heninger et al. (1984) observed prolactin and growth hormone responses to IV administration of tryptophan (7 g). We now report further data on the neuroendocrine and behavioral effects of IV tryptophan, including a description of the dose-response characteristics.

Methods

Subjects. We studied 11 healthy male subjects ranging in age from 22 to 31 years, with a mean age of 27.4 ± 1.3 (SEM) years. The subjects' weights were within 10% of ideal body weight in all cases (range: 63.6–87.3 kg, mean weight: 75.3 ± 3.5 kg). All subjects were in good health, not using any medication and were completely drug-free for at least 7 days prior to the start of the study. They were without personal or family history of psychiatric illness. All subjects freely participated after full informed consent was obtained.

Procedures. For each subject, tryptophan or saline infusion was performed on four occasions, with at least a 7-day interval between each test. The studies were carried out at the Clinical Research Center of the Hospital of the University of Pennsylvania. At 08.00 hours, after an overnight fast, the subjects were placed recumbant in bed, and a 19-gauge butterfly IV catheter connected to two 3-way stopcocks in series was inserted under sterile conditions into an antecubital vein. An infusion of normal saline, at a rate sufficient to keep the vein open, was started immediately. Three blood samples (12 ml each) were obtained at 15-min intervals to determine basal concentrations of prolactin, growth hormone, cortisol and thyrotropin (TSH).

L-Tryptophan was obtained in powdered form, and solutions were formulated, sterilized by milipore filtration and tested for pyrogenicity by the Hospital Pharmacy Service. Preliminary studies carried out in four subjects indicated that tryptophan infusions of 1.25 and 2.5 g were ineffective in stimulating hormone secretion. Therefore, in the present study, we employed doses of 5.0 g (dissolved in 500 ml normal saline), 7.5 g (in 1 l) and 10.0 g (in 1 l). Four trials were carried out in the following order: tryptophan 5.0 g, 7.5 g, 10.0 g, and normal saline (1 l). Subjects were aware of the substance being infused for each trial. Infusion of 5.0 g and 10.0 g took approximately 30 min. Blood samples were collected at 15, 30, 45, 60, 75, 90, 105 and 120 min after the start of an infusion. The use of the two 3-way stopcocks allowed the tryptophan or saline infusion to be stopped briefly during collection of the 15- and 30-min samples.

Hormone assay. PRL, GH and TSH concentrations were determined by means of double antibody radioimmunoassay techniques, and cortisol by means of a single antibody radioimmunoassay technique, as described previously (Winokur et al. 1982). All samples from all four trials for a single subject were analyzed in duplicate in the same assay.

Behavioral measurements. Estimates of changes in the subjects' emotional state during the various infusions were recorded using a series of 100 mm line tests composed of 16 items (Norris 1971). To facilitate data analysis, the 16 individual items were grouped into four categories: mental sedation (alert-drowsy, clear headed-fuzzy, quick witted-mentally slow, attentive-dreamy); physical sedation (strong-feeble, well coordinated-clumsy, energetic-lazy, capable-incompetent); tranquilization (calm-exited, contented-discontented, peaceful-agitated, relaxed-tense); and other (happy-sad, amicable-antagonistic, interested-bored, talkative-withdrawn). In addition, all subjects were administered the digit-symbol substitution test (DSST) and the symbol copying test at repeated intervals. The DSST required subjects to draw a symbol beneath a sample digit that corresponds to a code of associated symbols and digits at the top of the test form. The test is part of the Wechsler Adult Intelligence Scale (Wechsler 1955), except that the code was changed each time that the test was administered, and was a measure of a combination of information processing, scanning ability, and motor speed. The test was scored as the number of correct items completed in 90 s. The symbol copying test required subjects to copy the symbols used in the DSST. The test was scored as the number of items completed in 90 s. All three tests were administered at three time points (5 min before, 20 min after and 115 min after the start of an infusion) during each trial. An additional test trial was carried out 25 min before the start of the first (5.0 g) infusion.

Data analysis. The term "basal" is used to refer to the hormonal concentration at 0 min, immediately before the start of a tryptophan or a saline infusion. The symbol Δ (as in ΔGH) indicates the maximum increase above the basal value. Variations in hormone concentrations caused by tryptophan were examined over time by analysis of variance, and each individual time point was compared with basal values using Dunnett's test (Dunnett 1955). Changes in performance on the DSST and symbol copying test were also examined using analysis of variance. Data obtained from the analog mood scales were analyzed using the Mann-Whitney nonparametric test.

Results

Basal hormone concentrations. Serum concentrations of PRL, GH and cortisol at time 0 (immediately before the start of tryptophan or saline infusion) for each of the four trials are presented in Table 1. Mean basal cortisol levels

Table 1. Basal hormone concentrations[a]

	Tryptophan			
	Saline	5 g	7.5 g	10.0 g
Growth hormone[b]	1.8±0.2	1.9±0.2	2.3±0.6	2.5±0.4
Prolactin[b]	8.8±1.5	8.4±1.4	9.5±1.6	8.6±1.2
Cortisol[c]	11.6±1.5	17.8±2.3	13.0±1.2	12.1±1.8
TSH[b]	2.2±0.1	2.2±0.1	2.2±0.1	2.3±0.2

[a] Values represent the mean hormone concentration prior to the infusion of each dose of tryptophan or saline±SEM. The number of subjects examined was 11, except for TSH, where $N=6$

[b] Values do not differ significantly from each other according to analysis of variance, $P>0.05$

[c] Values differ significantly according to analysis of variance, $F(3.30)=>0.22$, $P<0.001$

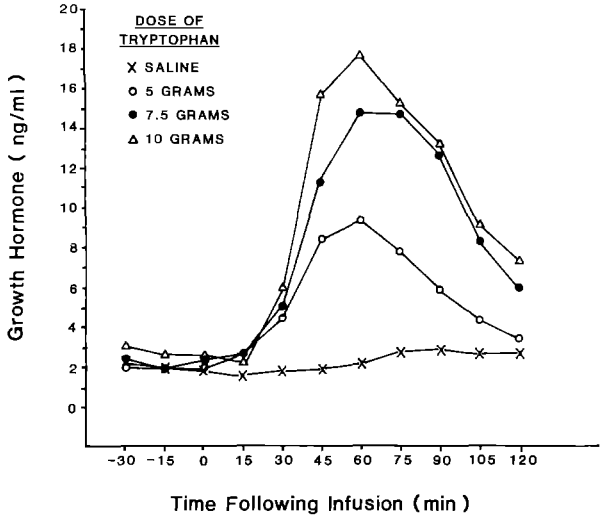

Fig. 1. Dose-effect curve for the release of growth hormone following the IV infusion of L-tryptophan. Subjects ($N=11$) were acclimated to the hospital bed for 30 min. L-Tryptophan or saline (0.9%) was then infused over a 20–25 min period starting at Time 0. Plasma samples were obtained every 15 min for measurement of growth hormone concentration

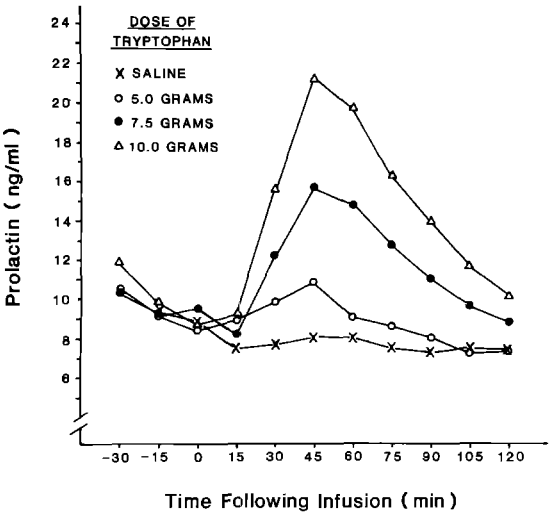

Fig. 2. Dose-effect curve for the release of prolactin following the intravenous infusion of L-tryptophan. See Fig. 1 for further details

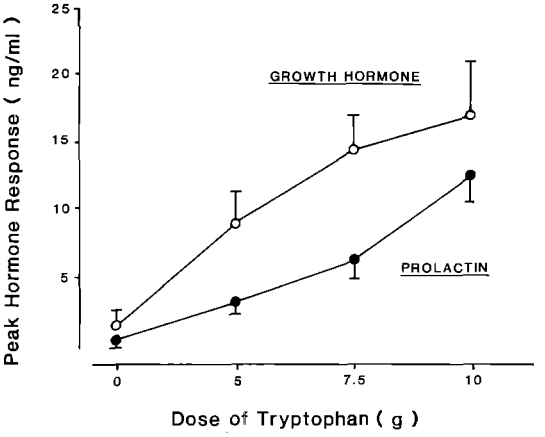

Fig. 3. Peak response of growth hormone and prolactin to infusion of L-tryptophan. The peak response for each subject was defined as the largest increase in hormone concentration above baseline values following infusion. The values represent hormone concentration with vertical lines indicating SEM

were significantly higher before infusion of tryptophan (7.5 g) than for any of the other three trials. No differences were observed across the four sessions for basal concentrations of PRL or GH. TSH concentrations at time 0 were generally close to or at the limit of detection for the assay for all trials (data not shown).

Hormone response to infusion with tryptophan or saline. Infusion of L-tryptophan at doses of 5.0, 7.5 or 10.0 g produced significant increases in GH concentration; whereas no change in GH levels was observed after saline infusion (Fig. 1). The peak plasma concentrations of GH were reached approximately 60 min after the start of the tryptophan infusion. GH levels were elevated significantly above preinfusion basal values between 45 and 75 min following the administration of tryptophan (5.0 g), and between 45 and 105 min following administration of tryptophan (7.5 and 10.0 g). Examination of the maximum GH response (ΔGH) revealed increasing response values between 5.0 and 10.0 g. However, the difference in ΔGH between the 7.5 g and 10.0 g trials was not statistically significant. Using an arbitrary cut-off value of $\Delta GH \geq 5.0$ ng/ml to define a response, eight subjects (73%) showed a GH response to tryptophan (5.0 g), nine subjects (82%) responded to a dose of 7.5 g and ten subjects (91%) responded to a dose of 10.0 g. One subject (9%) showed a ΔGH of >5.0 ng/ml during saline infusion.

Significant increases in PRL levels were observed after all three doses of L-tryptophan, but not after saline infusion (Fig. 2). The peak PRL response appeared at approximately 45 min after the start of the tryptophan infusion, somewhat earlier than the peak GH response. PRL levels were significantly elevated above basal concentrations at 45 min with 5.0 g tryptophan, between 30 and 75 min following 7.5 g, and between 30 and 90 min after the 10.0 g dose. Examination of ΔPRL after the three doses revealed a strong dose-response relationship (Fig. 3). Using a $\Delta PRL \geq 5.0$ ng/ml, two subjects (18%) responded to a dose of 5.0 g, six subjects (55%) responded to a dose of 7.5 g, and ten subjects (91%) responded to 10.0 g. No subject had a $\Delta PRL \geq 5.0$ ng/ml during saline infusion.

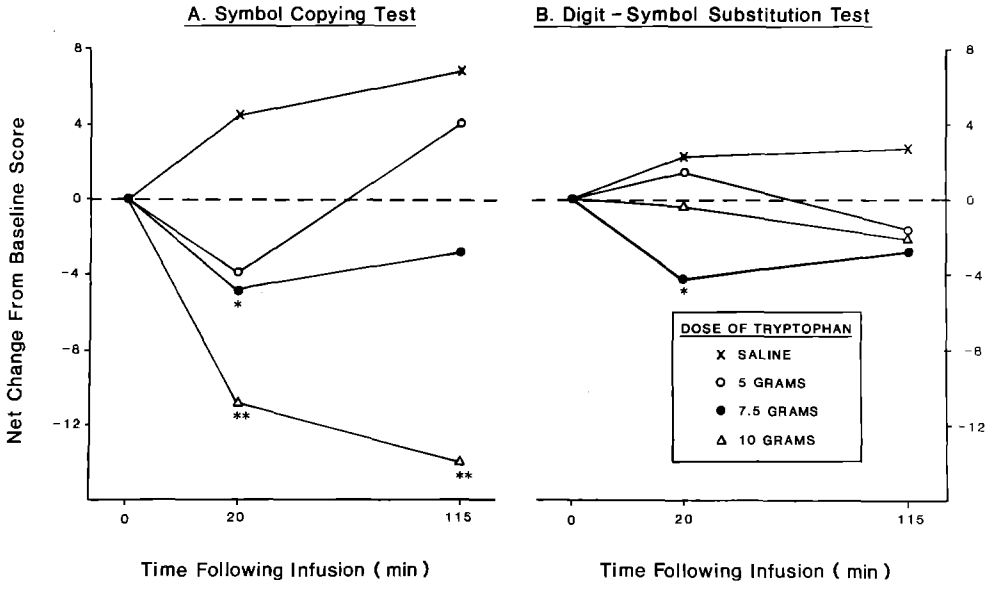

Fig. 4. Effect of the infusion of L-tryptophan on performance on the symbol copying test (Panel **A**) and the digit-symbol substitution test (DSST, Panel **B**). The two psychomotor tests were administered at three intervals: 1) at baseline just prior to infusion; 2) 20 min after infusion; and 3) 115 min after infusion. The values shown represent the mean net change from the baseline score determined for that particular dose of L-tryptophan. *Asterisk* indicates that the value differs significantly from that obtained following the administration of saline according to Student's *t*-test ($*P<0.05$; $**P<0.01$). The overall baseline value for symbol copying was 140.6 ± 8.2 items/90 s ($X\pm SEM$) and did not differ significantly between test sessions ($P>0.05$). The overall baseline value for the DSST was 62.0 ± 3.8 and did not differ significantly between test sessions ($P>0.05$)

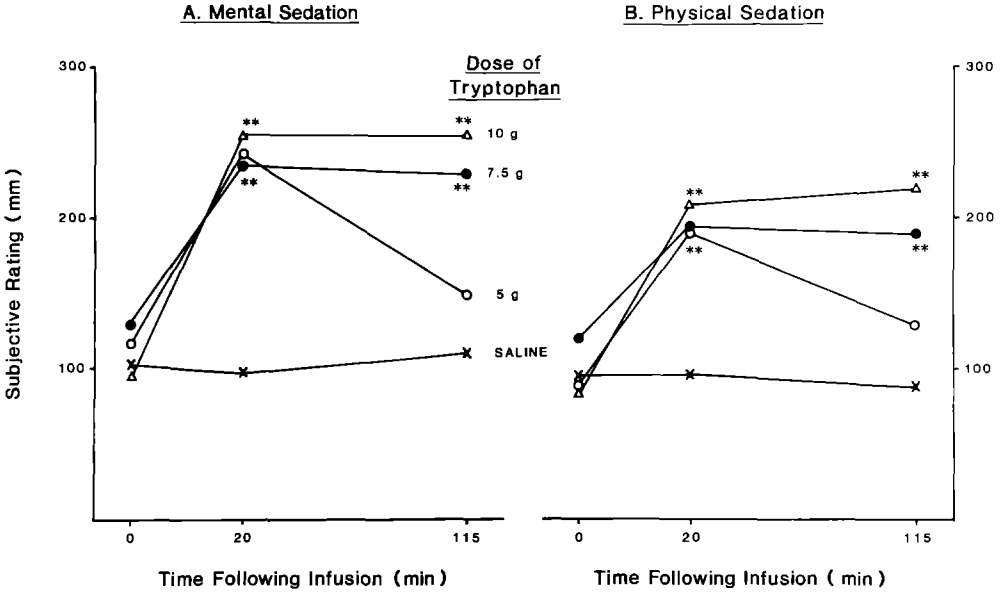

Fig. 5. Effect of the infusion of L-tryptophan on subjective ratings of mental sedation (Panel **A**) and physical sedation (Panel **B**). The administration of the tests is described in the legend of Fig. 4. The values shown represent the mean scale value (mm) far each dose of L-tryptophan. The *asterisk* indicates that the value differs significantly from that measured following saline administration according to Student's *t*-test ($*P<0.05$; $**P<0.01$)

Cortisol and TSH serum levels were monitored during the course of the four trials. No significant changes in plasma concentration were measured for either hormone at any time following the infusion of tryptophan (data not shown). Consistent with its known diurnal pattern of secretion (Weitzman et al. 1971), cortisol levels tended to decline during the course of the tryptophan and saline infusions.

Performance tests and subjective mood states. The effect of L-tryptophan infusion on scores of the two performance tests, the symbol copying test and the digit-symbol substitution test (DSST), are shown in Fig. 4. Tryptophan produced a dose-dependent impairment in performance on the symbol copying test when measured 30 min after the start of the infusion. The greatest impairment of symbol copying was produced by 10 g tryptophan, persisting 90 min after the infusion. In contrast, performance on the DSST was generally not significantly changed by tryptophan, except with 7.5 g tryptophan measured 30 min after the infusion.

The subjective mood states reported by the subjects on analogue rating scales were quite sensitive to change following the administration of tryptophan. All three doses of tryptophan produced significant increases in ratings of mental sedation at 30 min (Fig. 5). Significant effects on

mental sedation were observed at 105 min after 7.5 and 10.0 g tryptophan. Symptoms of physical sedation were also reported to be increased significantly following administration of all doses of tryptophan at 30 min. Effects of physical sedation persisted until 105 min following 7.5 and 10.0 g tryptophan. No significant changes on tranquilization were noted after the administration of tryptophan.

Side effects. No persistent side effects or untoward reactions were observed after any dose of L-tryptophan. Reports of sleepiness and lightheadedness were observed at all doses. At 10.0 g, five subjects felt queasy, with two subjects experiencing nausea. This side effect occurred infrequently at lower doses of tryptophan. Three subjects also reported tingling sensations in their arms and hands at 10.0 g.

Discussion

Infusion of L-tryptophan in doses of 5.0, 7.5 and 10.0 g resulted in significant increases in plasma concentrations of GH and PRL. Doses lower than 5.0 g were ineffective in stimulating hormone response, suggesting that a threshold concentration is necessary in order to obtain demonstrable effects. A linear dose-response relationship was observed for ΔPRL between 5.0 and 10.0 g L-tryptophan, with no diminishing efficacy at the maximum dose employed in the present study. In contrast, ΔGH increased significantly between the 5.0 and 7.5 g doses, but showed only a modest additional increment, which did not reach statistical significance, after 10.0 g tryptophan. In contrast to the stimulaltion of GH and PRL, L-tryptophan produced no increase in the concentrations of cortisol and TSH with any of the doses employed in this study. This observation lends support to the specific nature of the PRL and GH responses to tryptophan, since cortisol is highly responsive to a variety of stimuli and stressful conditions (Mason 1968).

The results of the present study are in substantial agreement with the previous reports of Charney et al. (1982) and of Heninger et al. (1984). Charney et al. (1982) infused tryptophan (7.0 g) to ten subjects and observed significant increases in plasma concentrations of both PRL and GH. PRL responses (>4 ng/ml above baseline) were observed in all ten subjects, whereas only six subjects had significant GH responses. Heninger et al. (1984) employed a similar protocol, with infusion of tryptophan (7.0 g) to 12 female and seven male control subjects. Significant elevations in PRL after tryptophan were observed in both male and female groups, although females demonstrated a larger ΔPRL. In the study of Heninger et al. (1984), depressed patients showed a lower PRL response to tryptophan than did sex-matched controls.

Previous inconsistent findings regarding the ability of L-tryptophan to stimulate hormonal secretion may be attributable to differences in such factors as dose, route of administration, nutritional status, sex and age. Utilization of the IV route of administration for L-tryptophan, which avoids the first-pass effect, may enhance the likelihood of obtaining significant activation of CNS serotonergic mechanisms. The consistency of the results observed by Charney et al. (1982), Heninger (1984) and our own group support the potential utility of IV L-tryptophan as a neuroendocrine stimulation test.

The lack of cortisol response to tryptophan infusion in the present study is in contrast to several preclinical and clinical studies demonstrating that stimulation of serotonergic systems results in increased cortisol secretion. Recently, Meltzer et al. (1984) reported that administration of 5-HTP (200 mg) produced a larger cortisol response in depressed, manic and schizoaffective patients than in healthy volunteers. Interestingly, the magnitude of the cortisol response to 5-HTP in the control group was small, and not statistically different than that observed after placebo administration. Thus, administration of precursors of serotonin biosynthesis (either tryptophan or 5-HTP) may produce limited or no change in cortisol secretion in healthy subjects, at least in the doses employed in the present studies. Cortisol responses to 5-HTP in depression may reflect alterations in CNS serotonergic activity, leading to enhanced responsiveness of 5-HT receptors. Further studies are needed to examine the cortisol response to serotonergic stimulants in both normal subjects and depressed patients.

Behavioral changes were observed after all three doses of tryptophan, with increases in symtoms related to mental sedation and physical sedation. The effects were of short duration after 5.0 g, but were still readily apparent 105 min after administration of the 7.5 and 10.0 g doses. In observing the subjects during the course of the trials, two phases of sedation were noted with the 10.0 g infusion. Pronounced feelings of sedation occurred in most subjects during the second half of the infusion (i.e., 15–30 min after the start of infusion). These symptoms diminished soon after the infusion was completed, and most subjects reported feeling more alert and clear-headed for the next 60 min. However, a second phase of sedation occurred at about 90 min after the initiation of tryptophan infusion. Several subjects reported feeling significantly drowsy and fatigued for several hours after the termination of the infusion.

Greenwood et al. (1974) examined the effects of IV L-tryptophan infusion (100 mg/kg delivered over a 3-h period) on a number of behavioral parameters. A pronounced increase in symptoms related to drowsiness and fatigue was observed, but minimal alterations in other aspects of mood state were noted. Charney et al. (1982) reported significant behavioral effects after the administration of tryptophan (7.0 g, IV). Nine of ten subjects reported a substantial increase in drowsiness, and six subjects reported a sense of feeling mellow and high. While sedation was clearly evident in the majority of our subjects, reports of enhanced mood state or feeling mellow were rare. Behavioral effects in the study of Charney et al. (1982) were observed under double-blind conditions; whereas our own observations were made under open conditions.

Performance on the DSST required the combined skills of symbol encoding, visual scanning ability and motor speed. The accompanying symbol copying test requires persistent motor performance that must be sustained for the entire 90-s testing period. The significant impairments in symbol copying ability, without concomitant reductions in DSST performance, suggest that the ability of subjects to sustain a high rate of motor performance over time was impaired by tryptophan, although their cognitive abilities remained intact. Furthermore, the dose-dependent relationship of symbol copying behavior and subjective reports of sedation suggest that objective performance tests may provide a useful direct measure of the pharmacological effects produced by serotonin precursors in humans. The assess-

ment of the behavioral effects of tryptophan in depressed patients may be especially interesting, in view of changes in the behavioral effects of serotonin agonists in animals produced by the chronic administration of antidepressant drugs (Lucki and Frazer 1985).

The results from the present study, in conjunction with several previous reports (Charney et al. 1982; Charney et al. 1984; Heninger et al. 1984) suggest that the IV administration of large doses of L-tryptophan can be of value as a provocative neuroendocrine challenge test. In light of the interest in altered serotonergic mechanisms in depression, this test might be of value of studies of patients with affective disorders. Indeed, reports utilizing this strategy with depressed patients have already appeared (Charney et al. 1984; Heninger et al. 1984). It must be noted that the stimulation of GH and PRL secretion by administration of L-tryptophan has not been established to occur through activation of CNS serotonergic mechanisms. As has been emphasized by other investigators (van Praag 1978; Charney et al. 1982; Meltzer et al. 1982; Heninger et al. 1984), tryptophan might influence hormone secretion as a consequence of peripheral effects or of effects mediated centrally through other neurotransmitter systems. Further studies are needed to standardize the L-tryptophan stimulation test, to compare the effects of L-tryptophan on hormonal secretion with those of serotonin receptor agonists, and to demonstrate blockade of tryptophan-induced hormone secretion by serotonin receptor blocking agents.

Acknowledgements. This research was supported by Research Scientist Development Award MH-00044 from the National Institute of Mental Health (Dr. Winokur), Public Health Service grants MH-37787 and MH-36262 (Dr. Lucki), Clinical Research Center grant NIH-5-MO1-RR00040 and MH-05989-28 (Mr. Lindberg).

Cordelia Shute, R.N. and the staff of the Clinical Research Center, Hospital of the University of Pennsylvania, provided nursing care. William Judd, of the Pharmacy and Drug Information Service, Hospital of the University of Pennsylvania, prepared the tryptophan for infusion. Phyllis H. Smith assisted in preparing the manuscript.

References

Anton-Tay F, Wurtman RJ (1971) Brain monoamines and endocrine function. In: Martini L, Ganong WF (eds) Frontiers in neuroendocrinology, Oxford University Press, New York, pp 45–66

Ashcroft GW, Crawford TBB, Eccleston D, Sharman DF, McDougall EJ, Stanton JG, Binns JK (1966) 5-hydroxyindole compounds in the cerebrospinal fluid of patients with psychiatric or neurological diseases. Lancet 2:1049–1052

Bergstrom DA, Kellar KJ (1979) Adrenergic and serotonergic receptor binding in rat brain after chronic desmethylimpramine treatment. J Pharmacol Exp Ther 209:256–261

Bunney WE Jr, Davis JM (1965) Norepinephrine in depressive reactions. Arch Gen Psychiatry 13:483–494

Charney DS, Heninger GR, Reinhard JF (1982) The effect of intravenous L-tryptophan on prolactin and growth hormone and mood in healthy subjects. Psychopharmacology 77:217–222

Charney DS, Heninger GR, Sternberg DE (1984) Serotonin function and mechanism of action of antidepressant treatment. Arch Gen Psychiatry 41:359–365

Coppen AJ (1967) The biochemistry of affective disorder. Br J Psychiatry 113:1237–1264

Coppen A, Eccleston EG, Peet M (1973) Total and free tryptophan concentration in the plasma of depressive patients. Lancet 2:60–63

Curzon G, Kantameneni BD, Van Boxel P, Gillman PK, Bartlett JR, Bridges PK (1980) Substances related to 5-hydroxytryptamine in plasma and in lumbar and ventricular fluids of psychiatric patients. Acta Psychiatr Suppl 280:3–19

Dunnett CW (1955) A multiple comparison procedure for comparing several treatments with a control. J Am Stat Assoc 50:1096–1121

Faber J, Hagen C, Kirkegaard C, Lauridsen UB, Muller SE (1977) Lack of effects of L-tryptophan on basal and TRH-stimulated TSH and prolactin levels. Psychoneuroendocrinology 2:413–415

Fernstrom JD, Wurtman RJ (1971) Brain serotonin content: Physiological dependence on plasma tryptophan levels. Science 173:149–152

Fernstrom JD, Wurtman RJ (1972) Brain serotonin content: Physiological regulation by plasma neutral amino acids. Science 178:414–416

Fraser WM, Tucker HSt, Grubb SR, Wigand JP, Blackard WG (1979) Effect of L-tryptophan on growth hormone and prolactin release in normal volunteers and patients with secretory pituitary tumors. Horm Metab Res 11:149–155

Fuxe K, Butcher LL, Engel J (1971) DL-5-Hydroxytryptophan-induced changes in central monoamine neurons after peripheral decarboxylase inhibition. J Pharm Pharmacol 23:420–424

Gillman PK, Bartlett JR, Bridges PK, Kantameneni BD, Curzon G (1980) Relationship between tryptophan concentrations in human plasma, cerebrospinal fluid and cerebral cortex following tryptophan infusion. Neuropharmacology 19:1241–1242

Glass AR, Smallridge RC, Schaff M, Diamond RC (1980) Absent prolactin response to L-tryptophan in normal and acromegalic subjects. Psychoneuroendocrinology 5:261–265

Greenwood MH, Friedel J, Bond AJ, Curzon G, Lader MH (1974) The acute effects of intravenous infusion of L-tryptophan in normal subjects. Clin Pharmacol Ther 16:455–464

Handwerger S, Plonk JW, Lebovitz HE, Bivens CH, Feldman JM (1975) Failure of 5-hydroxytryptophan to stimulate prolactin and growth hormone secretion in man. Horm Metab Res 7:214–216

Heninger GR, Charney DS, Sternberg DE (1984) Serotonergic function in depression. Arch Gen Psychiatry 41:398–402

Imura H, Nakai Y, Yoshimi T (1973) Effect of 5-hydroxytryptophan (5-HTP) on growth hormone and ACTH release in man. J Clin Endocrinol Metab 36:204

Kato Y, Nakai Y, Imura H, Chihara K, Ohgo S (1974) Effect of 5-hydroxytryptophan (5-HTP) on plasma prolactin levels in man. J Clin Endocrinol Metab

Lal S, Young SN, Cervantes P, Guyda H (1980) Effect of L-tryptophan on apomorphine-induced growth hormone secretion in normal subjects. Pharmakopsychiatrie 13:331–335

Lancranjan I, Wirz-Justice A, Puhringer D, Del Pozo E (1977) Effect of L-v-hydroxytryptophan unfusion on growth hormone, and prolactin secretion in man. J Clin Endocrinol Metab 45:588–593

Lapin IP, Oxenkrug GF (1969) Intensification of the central serotonergic processes as a possible determinant of thymoleptic effect. Lancet 1:132–136

Lucki I, Frazer A (1985) Changes in behavior associated with serotonin receptors following repeated treatment of rats with antidepressant drugs. In: Seiden LS, Balster RL (eds) Alan Liss Co, New York, pp 339–357

MacIndoe JH, Turkington RW (1973) Stimulation of human prolactin secretion by intravenous infusion of L-tryptophan. J Clin Invest 52:1972–1978

Mason JW (1968) A review of psychoendocrine research on the pituitary-adrenal cortical system. Psychosom Med 30:576–607

Meltzer HY, Wiita B, Tricou BJ (1982) Effect of serotonin precursors and serotonin agonists on plasma hormone levels. In: Ho BT, Schoolar JC, Usdin E (eds) Serotonin in biological psychiatry. Raven Press, New York, pp 117–138

Meltzer HY, Lowy M, Robertson A, Goodnick KP, Perline R (1984) Effect of 5-hydroxytryptophan on serum cortisol levels

in major affective disorders III. Effect of antidepressants and lithium carbonate. Arch Gen Psychiatry 41:391–397
Modlinger RS, Schonmueller JM, Arora SP (1980) Adrenocorticotropin release by tryptophan in man. J Clin Endocrinol Metab 50:360–363
Mueller EE, Brambilla F, Cavagnini F, Peracchi M, Panerai A (1974) Slight effect of L-tryptophan on growth hormone release in normal human subjects. J Clin Endocrinol Metab 39:1–5
Norris H (1977) The action of sedatives on brain stem oculomotor systems in man. Neuropharmacology 10:181–191
Pare CMB, Sandler M (1959) A clinical and biochemical study of a trial of iproniazid in the treatment of depression. J Neurol Neurosurg Psychiatry 22:247–251
Peroutka SJ, Snyder SH (1980) Chronic antidepressant treatment lowers spiroperidal-labeled serotonin receptor binding. Science 210:88–90
van Praag HM (1974) Central monoamine deficiency in depressions: Causative or secondary phenomenon. Pharmakopsychiatry 8:321–326
van Praag HM (1978) Amine hypothesis of affective disorders. In: Iversen LL, Iversen SD, Snyder SH (eds) Biology of mood and antianxiety drugs, vol 13. Plenum Press, New York, pp 187–297
van Praag HM, Korf J, Puite J (1970) 5-Hydroxyindoleacetic acid levels in the cerebrospinal fluid of depressive patients treated with probenecid. Nature 225:1259–1260
Savage DD, Mendels J, Frazer A (1980) Monoamine oxidase inhibitors and serotonin uptake inhibitors: differential effects of [H^3] serotonin binding sites in rat brain. J Pharmacol Exp Ther 212:259–263
Schildkraut JJ (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 122:509–522
Segal DS, Kuczenski R, Mandell DJ (1974) Theoretical implications of drug-induced regulation for a biogenic amine hypothesis of affective disorder. Biol Psychiatry 9:147–159
Smythe GA, Compton PJ, Lazaru L (1976) Serotonergic control of human growth hormone secretion: The actions of L-dopa and z-bromoergocrytise. In: Pecile A, Muller EE (eds) Growth hormone and related peptides. Excerpta Medica, Amsterdam, pp 222–235
Strom-Olsen R, Weil Malherbe H (1958) Humoral changes in manic-depressive psychosis with particular reference to excretion of catecholamines in urine. J Ment Sci 104:696–704
Wechsler D (1955) Manual for the wechsler adult intelligence scale. The Psychological Corporation, New York
Weitzman ED, Fukashima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L (1971) The twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. J Clin Endocrinol Metab 33:14–22
Westenberg HGM, van Praag HM, de Jong JTVM, Thijssen JHH (1982) Postsynaptic serotonergic activity in depressive patients: evaluation of the neuroendocrine strategy. Psychiatr Res 7:361–371
Winokur A, Amsterdam JD, Caroff S, Snyder PJ, Brunswick D (1982) Variability in hormonal response to a series of neuroendocrine challenges (TRH, GnRH, ITT, DST) in depressed patients. Am J Psychiatry 139:39–44
Wirz-Justice A, Purhringer W, Lacoste V, Graw P, Gastpar M (1976) Intravenous 1-5-hydroxytryptophan in normal subjects: an interdisciplinary precursor loading study. Pharmakopsychiatrie 9:277–288
Woolf PD, Lee L (1977) Effect of the serotonin precursor, tryptophan, on pituitary hormone secretion. J Clin Endocrinol Metab 45:123–133

Received March 28, 1985; Final version July 17, 1985