Lack of Relapse With Tryptophan Depletion Following Successful Treatment With ECT

Frederick Cassidy, M.D., Elizabeth Murry, M.D., Richard D. Weiner, M.D., Ph.D., and Bernard J. Carroll, M.B., Ph.D.

Objective: Although the antidepressant mechanism of ECT is unknown, there are considerable data to support serotonergic involvement. The effects of tryptophan depletion were studied in patients with major depression treated successfully with ECT. Method: Five patients who had been successfully treated with ECT for major depression were studied in a randomized, double-blind, crossover design comparing tryptophan depletion to a placebo procedure. Results: No effect of tryptophan depletion on mood symptoms was observed despite more than an 85% decrease in total serum tryptophan. Conclusions: These data suggest that presynaptic serotonin availability may not be necessary for the acute maintenance of an antidepressant response to ECT.

(Am J Psychiatry 1997; 154:1151–1152)

While ECT remains the most effective treatment for major depression, its mechanism of action is unclear. Serotonergic systems, as well as other neurotransmitter systems, have been implicated (1). Studies of serotonergic changes during ECT have employed animal models or relied on changes in 5-hydroxyindoleacetic acid in CSF. Delgado et al. (2) demonstrated the value of tryptophan depletion as a methodology for studying serotonergic systems in vivo by applying this procedure to patients who had recently responded to antidepressant drug treatment for major depression and demonstrating the transient reappearance of depressive symptoms. In an extension of this work, Salomon et al. (3) showed that reemergence of symptoms was dependent on the relative serotonergic properties of the medication, i.e., patients treated successfully with serotonergic antidepressants tended to relapse, while patients treated with more noradrenergic ones did not.

Although initially applied to the study of antidepressant medication, the probe is also pertinent to the study of other therapies, such as ECT, that are hypothesized to act through the serotonergic systems.

Received June 12, 1996; revision received Feb. 18, 1997; accepted April 4, 1997. From the Department of Psychiatry and Behavioral Sciences, Duke University; and John Umstead Hospital, Butner, N.C. Address reprint requests to Dr. Cassidy, Box 3414, Duke University Medical Center, Durham, NC 27710.

Supported in part by NIMH Mental Health Clinical Research Center grant MH-40159.

Pedro Delgado, M.D., provided advice on logistic and procedural details of the tryptophan depletion protocol.

METHOD

Subjects were recruited from the inpatient mood disorders service at John Umstead Hospital. All subjects met DSM-IV criteria for major depressive episode at the time they were evaluated for ECT and had subsequently responded to a course of bilateral ECT as documented by both clinical impression and at least a 65% decrease in scores on the Montgomery-Åsberg Depression Rating Scale (mean= 87.0%, SD=13.2%). All subjects gave written informed consent for participation in this study.

The study group comprised three white women and one white and one Oriental man. All met DSM-IV criteria for major depressive episode, three with psychotic features. The mean age was 40.6 years (SD=11.2, range=22–52). Immediately before ECT, subjects were treated with the following: nortriptyline; nortriptyline, haloperidol, and lorazepam; imipramine and loxitane; venlafaxine; and fluphenazine and lorazepam.

All subjects received standard bilateral, brief-pulse ECT through use of a MECTA model SR-1 ECT device. Stimulus intensity was titrated at the first treatment to achieve a 25-second motor convulsion. Men initially received a 80-mC stimulus and women a 48-mC stimulus, and stimulus charge increased by 50% until an adequate motor convulsion was obtained. The subsequent treatments employed a stimulus charge 50% above the determined threshold and were thereafter increased by 50% as needed to maintain a motor convulsion for 25 seconds or longer. Subjects received methohexital and succinylcholine before stimulus, beginning at doses of 1 mg/kg, which were adjusted as needed. Four subjects were premedicated with glycopyrrolate as a vagolytic agent. One patient received midazolam after the third and subsequent treatments for postictal agitation. Psychotropic medications were discontinued before treatment. Subjects received treatments three times per week until a therapeutic plateau had been achieved, as determined by the treating psychiatrist and the ECT team. The mean number of treatments received was 13 (SD=2, range=11–15).

The study used a double-blind, counterbalanced, placebo-controlled design over a 5-day period beginning 1–4 days after completion of ECT (mean=2, SD=1), before the institution of maintenance psychotropic medication. Days 1, 3, and 5 were used to establish and

TABLE 1. Montgomery-Åsberg Depression Rating Scale Scores and Serum Tryptophan Levels for Five Patients With Major Depression Treated With ECT and Subsequent Crossover Comparison of Tryptophan Depletion and Placebo Procedure

		Depression Scale Score					Mean Tryptophan Level (nmol/ml)			
			Placebo		Amino Acid Mixture		Placebo		Amino Acid Mixture	
Patient	Order of Crossover Treatments[a]	Before ECT	Baseline	After 5 Hours	Baseline	After 5 Hours	Baseline	After 5 Hours	Baseline	After 5 Hours
1	P:A	23	3	2	2	2	60.4	40.6	60.9	4.6
2	P:A	29	8	10	10	9	38.8	41.0	34.7	6.8
3	P:A	44	2	1	2	2	38.7	35.7	43.5	4.5
4	A:P	50	8	4	2	1	50.0	45.8	52.8	5.3
5	A:P	44	3	3	5	4	32.9	33.4	31.0	8.7
Total group										
Mean		38.0	4.8	4.0	4.2	3.6	44.2	39.3	44.6	6.0
SD		11.4	2.9	3.5	3.5	3.2	11.0	4.9	12.4	1.8

[a]Indicates whether placebo (P) or amino acid mixture (A) was given first.

confirm that patients were at baseline; subjects were given a full-strength amino acid mixture or a control drink in blind, random order at 9:00 a.m. on days 2 and 4 of the experiment. Details of the depletion technique are described elsewhere (4). On days 2 and 4 ratings were obtained at 9:00 a.m., 10:00 a.m., 12:00 noon, 2:00 p.m., and 4:00 p.m. through use of the Montgomery-Åsberg Depression Rating Scale (5). Depression scale ratings were completed by one of us (F.C.), who remained blind throughout the protocol. Blood samples were obtained concurrently with each rating, and serum was frozen at –80°C for subsequent tryptophan analysis with high performance liquid chromatography (6). This assay is able to detect 1.5 nmol/ml of tryptophan. The coefficient of variation is less than 3%.

Changes in depression scale scores were analyzed to assess the effect of tryptophan depletion on mood state, as well as to test for order and period effects, through use of t tests (7).

RESULTS

No clinical change was noted during tryptophan depletion or control condition in any of the five subjects. A mean 85% decrease in tryptophan levels was noted after ingestion of the active mixture (table 1). Changes in depression scale scores during depletion were not significant (t=0.60, df=3). Analysis of changes in depression scale scores did not indicate either period (t=–0.60, df=3) or order (t=0.40, df=3) effects.

DISCUSSION

Although animal and human CSF studies document serotonergic changes during ECT (1), the role of serotonin in the therapeutic mechanism of ECT has never been demonstrated. Observed increases in 5-hydroxytryptamine ($5\text{-}HT_2$) receptor densities during electroconvulsive seizures are in contrast to those seen with antidepressant therapies (1), highlighting the importance of not prematurely attributing causality to observed changes. Tryptophan depletion strategies have permitted a more direct approach to the in vivo study of serotonergic systems. Tryptophan depletion, however, did not demonstrate a major role of presynaptic serotonin availability in the treatment of major depression with ECT. Although the possibility of a type II error was not excluded, a power analysis (8) of changes in Montgomery-Åsberg Depression Rating Scale scores indicated that more than 1,000 subjects would be required for a power of 0.80 at an alpha level of 0.05 to demonstrate a difference. For practical reasons, the study was not pursued further.

Clarification of the neurotransmitter systems responsible for the antidepressant efficacy of ECT is important to the rational selection of maintenance pharmacotherapy following ECT, as well as to the development of augmentation strategies for use during ECT. Further research of the mechanism of ECT is warranted.

REFERENCES

1. Sackeim HA, Devanand DP, Nobler MS: Electroconvulsive therapy, in Psychopharmacology: The Fourth Generation of Progress. Edited by Bloom FE, Kupfer DJ. New York, Raven Press, 1995, pp 1123–1141
2. Delgado P, Charney D, Price L, Aghajanian K, Landis H, Heninger G: Serotonergic function and the mechanism of antidepressant action. Arch Gen Psychiatry 1990; 47:411–418
3. Salomon R, Miller H, Delgado P, Charney D: The use of tryptophan depletion to evaluate central serotonin function in depression and other neuropsychiatric disorders. Int Clin Psychopharmacol 1993; 8:41–46
4. Cassidy F, Murry E, Carroll BJ: Tryptophan depletion in recently manic patients treated with lithium. Biol Psychiatry (in press)
5. Montgomery SA, Åsberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134:382–389
6. Berardino MB, Roingeard FC, Fukagawa NK: Plasma tryptophan and tyrosine concentrations: determination using high performance liquid chromatography and fluorometric detection. J Nutritional Biochemistry 1990; 1:220–222
7. Fleiss J: The Design and Analysis of Clinical Experiments, New York, John Wiley & Sons, 1986
8. Cohen J: Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Hillsdale, NJ, Lawrence Erlbaum Associates, 1988