Drug-Induced Actions on Brain Neurotransmitter Systems and Changes in the Behaviors and Emotions of Depressed Patients

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Despite cumulative evidence that the tricyclic drugs result in significant changes in the functioning of brain serotonergic (5-HT) and nordrenergic (NE) systems, such changes have not been found to be associated with recovery from depression. Based upon evidence that the 5-HT and NE systems were associated with different emotions, it was hypothesized that changes in these systems were associated with different components of behavior in drug-responsive patients and not with changes in the "whole" disorder. Findings from this multihospital study of 104 unipolar and bipolar depressed patients showed early drug-associated reductions in anxiety and hostility in treatment responders to precede changes in motor retardation and depressed mood. Adopting this approach of looking for relationships between changes in components of major depression and changes in neurotransmitter system function, decreases in 5-HT and NE metabolite concentrations in cerebrospinal fluid (CSF) in patients treated with tricyclics, were found to be correlated with changes in specific behaviors. Results indicated the following: (1) drug-induced changes in the 5-HT system to be associated with mood aspects, notably anxiety, and depressed mood; changes in NE primarily with the psychomotor, secondarily with the mood components of the depressed state; (2) the pattern of relationships between changes in 5-HT and in mood in the unipolar was different than that in the bipolar subtype. The results indicate that in determining the relationships of biochemical changes to behavioral ones, that it is important to take into account the type of depression (bipolar or unipolar), as well as examining individually and over time those components that make up the disorder of depression. These results support evidence that tricyclics have multiple behavioral actions, that response is mediated through changes in specific behaviors and that this approach warrants further application in prospective studies of antidepressant drug mechanisms and their therapeutic actions.
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KEY WORDS: *Antidepressants; Neurotransmitters; CSF metabolites; Behavior; Anxiety*

Despite thirty years of research on the mechanisms of action of the tricyclic drugs, it is unclear, as Delini-Stula (1991) has stated, how these drugs bring about recov-

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ery in severely depressed patients. Although they have major effects on the functioning of brain serotonergic (5-HT) and noradrenergic (NE) systems, their effects on these systems have not been shown to be directly associated with positive changes in the clinical disorder (Bowden et al. 1985). This lack of association between a clear change in CSF monoamine concentrations with explicit recovery leaves the relevance of these neurotransmitter changes to the therapeutic actions of the drugs open to question.

We (Katz and Maas 1994) have previously attributed the lack of clarity regarding the role of these neurotransmitter systems in depression partly to the failure to measure drug-associated changes in behavior with the same precision used to investigate biochemical changes. Although drug-induced changes in the global severity of the depressive disorder have been well documented in clinical trials of these agents, the actual sequence and type of changes in the component behaviors of treatment-responsive patients remains largely undefined.

A major aim of the collaborative study of the psychobiology of depression (Katz et al. 1979; Maas et al. 1980) was to investigate the mechanism of the therapeutic action of tricyclic antidepressant drugs. To identify drug actions that were specific to the therapeutic effects, the study focused on neurochemical and behavioral changes in treatment-responsive patients, in contrast to the pattern of change in nonresponsive patients.

With reference to the actions of tricyclic antidepressant drugs, this study of a multihospital sample of unipolar and bipolar depressed patients determined that the initial actions of the tricyclic drugs amitriptyline (AMI) and imipramine (IMI) in treatment-responsive patients were in reductions in anxiety and hostility prior to changes in depressed mood and retardation (Katz et al. 1987). The initial changes in anxiety and hostility were correlated with concentrations of AMI in plasma. We interpreted this sequence of changes during treatment as an initial "calming" effect followed within a week by a "stimulating" (reduction of retardation or increase of agitation) effect (Katz et al. 1991). The results supported the earlier observations of Kielholz (1968) that the efficacy of the drugs was based on multiple actions on the behavioral aspects of the disorder.

These findings further indicated that the actions of the tricyclics on 5-HT and NE systems were expressed through the specific components of depression rather than through changes in the disorder as defined globally. Evidence summarized earlier by Carlsson et al. (1976) that 5-HT and NE neurotransmitter systems were associated with the regulation of different behaviors has been supported by more recent work (e.g., the 5-HT system with aggression) (Jacobs et al. 1990; van Praag et al. 1986), 5-HT with anxiety (Kahn et al. 1988), and the NE system with psychomotor activation (Carlsson 1969), and with arousal and alarm (Redmond et al. 1986). These studies provided the background for the development of hypotheses in this study concerning how the effects of antidepressants on these systems result in therapeutic changes in depression.

To test hypotheses based on these previous data, we described the depressive disorder in terms of its behavioral, emotive, cognitive, and somatic components. Changes induced by the drugs were then measured through these components. More specifically, we hypothesized that in patients who responded to treatment: (1) changes in the functioning of the 5-HT system (as reflected in changes in the concentration of 5-hydroxyindoleacetic acid [5-HIAA] in CSF) would correlate with changes in hostility and in anxiety; and (2) changes in the NE system (reduction of 3-methoxy-4-hydroxyphenylglycol [MHPG] in CSF) would correlate with changes in "arousal" (anxiety, agitation, somatization) and psychomotor retardation. Most importantly, these relationships would *not* be found in patients not responsive to treatment. Lastly, because unipolar patients have been found to be significantly more anxious and agitated (Beigel and Murphy 1971; Katz et al. 1982), have higher baseline levels of urinary NE and epinephrine (Koslow et al. 1983), and different biochemical predictors of treatment response (Maas et al. 1984) than bipolar patients, we proposed (3) that relationships between biochemical and behavioral changes will be different in the two clinical subtypes.

METHODS

The methods employed in the National Institute of Mental Health collaborative study of the psychobiology of depression have been written in detail (Maas et al. 1980; Secunda et al. 1980; Katz et al. 1982). Issues relevant to this report will be briefly summarized.

All patients met the Research Diagnostic Criteria (Spitzer et al. 1978) for a major depressive episode of either the unipolar or bipolar type, as well as met the inclusion and exclusion criteria for primary affective disorder (Robins and Guze 1972). In this article, "depressed patients" represents unipolar and bipolar patients.

The data presented were obtained from 104 depressed patients who completed a baseline of 2 weeks of placebo and a 4-week period of drug treatment with either AMI or IMI. Secunda et al. (1980) have given details of the pretreatment and the drug treatment protocols. We assigned 125 patients to a particular drug on a random basis, 64 to AMI, and 61 to IMI; however, nine patients did not complete the AMI protocol, and 12 did not complete the IMI protocol (Secunda et al. 1980). Thus, of the 104 patients who completed treatment, 55 received AMI and 49 received IMI.

Twenty-six unipolar and 23 bipolar patients com-

Table 1. Methods for Measuring State and Outcome Constructs

I. Observational rating methods
  A. "Live" interview (clinical ratings)
    1. Hamilton Depression Rating Scale*
    2. SADS-Change Scale (SADS-C)
    3. Video Interview Behavior and Symptom Scale (VIBES)
  B. Video review (clinicians at different centers)
    1. Video Interview Behavior and Symptom Scale (VIBES)
    2. Ching K-S Social Behavior Scale
    3. Hamilton Depression Scale
  C. Ward behavior (nurse)
    1. Affective Disorder Rating Scale (ADRS)
    2. NIMH Mood Scale
    3. Global Ward Behavior Scale (GWBS)
II. Patient testing
  A. Self-report scales
    1. Symptom Checklist-90 (SCL-90)
    2. NIMH Mood Scale
  B. Psychomotor performance
    1. Reaction time
    2. Tapping speed
    3. Dot placing
    4. Tracking

* See text for literature references to scales.

pleted treatment with IMI. Thirty-eight unipolar and 17 bipolar patients completed the AMI protocol.

The drugs were administered double-blind, and the dose and schedule were fixed. The dose was raised to 250 mg/day by day seven of treatment. Some patients (13%) were unable to tolerate this dose, so it was decreased (to 100–200 mg/day).

The research protocol required that an evaluation of behavioral response be made weekly and at 2½ weeks, the expected height of the drug effect. After four weeks of drug treatment (the termination of the study), patients were categorized as responders (essentially recovered), or nonresponders (essentially unrecovered, or with minimal or no change), or as having indeterminate responses. The indeterminate group contained patients who had only a modest response to drug treatment, and also contained patients who with a longer period of treatment might have eventually met the criteria for recovery or nonrecovery.

Classification as a responder or nonresponder was based upon changes in several general indices of the severity of the depressive state (e.g., global scales of severity and improvement, and the Schedule for Affective Disorders and Schizophrenia [SADS]-Change Global Assessment Scale) (Katz et al. 1984; Maas et al. 1984).

Measurement of the Behavioral and Affect Components of the Depressed State

Based upon a review of research of the major components of behavior, affect, and expressivity in the clinical state (Katz et al. 1982, 1984), an extensive inventory of methods was applied for the "multivantaged" analysis of depression. Table 1 shows the several vantages and the methods that were used.

Psychometric analyses based on administration of these methods at baseline to a broad sample of patients with affective disorders and based on administration to healthy controls, resulted in the derivation of 11 state constructs that measure the major components of depression. The constructs include the disturbed emotions of depressed mood, anxiety, and hostility; abnormalities of motor movement (retardation, agitation, and distressed facial expression); maladaptive social behavior; interpersonal sensitivity; somatization (physical complaints and sleep disorder); and cognitive impairment, which includes both thinking and concentration problems.

Measures of the constructs were drawn from the scales representing each of the vantages. The "anxiety" construct was the result of combining four subfactors: the doctor ratings of anxiety from the live interview (Table 1) based on items from the Hamilton (1960), the SADS (Endicott and Spitzer 1978), and the VIBES (Katz et al. 1989); the nurses' factor ratings from the WBRS (Raskin et al. 1969) and the ADRS (Murphy et al. 1980); independent observer ratings from the video interview (VIBES); and the patient's self-report based on factors from the SCL-90 (Derogatis et al. 1974), and the National Institute of Mental Health (NIMH) Mood Scale (Raskin et al. 1969).

The factor structure, operational definitions of each of the constructs, and research on their reliability and validity have been published (Katz et al. 1982, 1984).

Measurement of behavior for assessment of

Table 2. Baseline and Treatment Values of CSF Amine Metabolites by Drug

	Drug	No. of Subjects	Baseline (pmol/ml)	Treatment (pmol/ml)	% Change
MHPG	AMI	34	49.7 ± 11.2[a]	28.7 ± 5.0[b]	−41
	IMI	31	45.7 ± 12.2	26.9 ± 5.0[b]	−39
5-HIAA	AMI	31	114.9 ± 39.2	70.6 ± 25.6[b]	−36
	IMI	29	117.9 ± 34.5	74.9 ± 24.5[b]	−35
HVA	AMI	31	178.6 ± 73.0	172.3 ± 81.3	−3
	IMI	29	179.6 ± 57.5	192.9 ± 94.0	+7

Note: Table from Bowden et al. 1985. Reprinted by permission. Baseline and treatment values are mean ± SD.
[a] Significant ($p < .02$) between values for AMI and IMI at baseline.
[b] Significant difference ($p < .0001$: paired t test) compared with baseline.

changes from baseline was initiated following the first week of treatment and conducted at 2, 2½, and 4 weeks during the treatment period.

Biochemical Assays

The neurotransmitter metabolites assayed were 5-HIAA, MHPG, and homovanillic acid (HVA). Levels of the metabolites in CSF were determined by selected ion monitoring (gas chromatography–mass spectrometry). Details of collection periods, collection methods, and analytic techniques are given by Secunda et al. (1980); a brief description follows:

Lumbar puncture (LP) was performed between 8:00 A.M. and 9:00 P.M. on protocol pretreatment placebo, day 11 and protocol, day 33 (after 18 days of treatment). The patient has been fasting overnight for 8 hours. The LP was performed with the patient in a sitting position. The 20-ml samples of CSF were kept on ice, then mixed, and divided into aliquots (blind replicates). Sodium metabisulfite and appropriate internal standards were added, and the samples were frozen at −70°C until analyzed.

All analyses of each substance were completed on coded replicate samples, blind to the subject's diagnosis. Assays on a particular substance were analyzed in a single laboratory, regardless of the center of origin.

The values of the CSF metabolites are expressed as picomoles per milliliter. Because of sample loss, failures in collection, and technical problems, every chemical value was not available for every patient.

Measurement of Drug and Metabolite Plasma Levels

We examined relationships between antidepressant drug levels, treatment response, and pretreatment neurotransmitter values. Concentrations of IMI and AMI and their metabolites, desmethylimipramine and nortriptyline, were determined in plasma and CSF. The plasma measures were obtained weekly during drug treatment, and the CSF measures were obtained after 18 to 21 days of treatment. The levels of drugs and their demethylated products were determined with gas chromatography–mass spectrometry. In addition to the values for the parent and demethylated drugs, the sum of the two, and the ratio of the demethylated to the parent compound was calculated. A detailed description of the protocol is given by Secunda et al. (1980); further reports are in Hanin et al. (1985), Kocsis et al. (1986), and Katz et al. (1991).

Plan of Analysis: Relationships between Drug-Induced Changes in the CSF Amine Metabolites and in Specific Behaviors

The values for the CSF amine metabolites in this sample of depressed patients, before and after 18 days of treatment with AMI or IMI are in Table 2 (Bowden et al. 1985). Concentrations of MHPG and 5-HIAA decreased significantly during treatment; by contrast, the level of HVA was the same before and after treatment. There were no differences reflected in the effects of AMI or IMI on MHPG and 5-HIAA levels.

To determine if these drug-induced decreases in CSF concentrations of MHPG and 5-HIAA were linearly related to drug associated changes in behavior at 2½ weeks of treatment (when steady-state concentrations of the drugs in plasma should have been reached), Pearson product–moment bivariate correlations and multiple regressions with the behavioral construct as the independent variable were computed. Residual values from the regression of scores at 2½ weeks on baseline scores were used as measures of change for the behavioral variables (Wittenborn 1966). Percentage of change was used to control for baseline scores for the biochemical measures because this value had been used in prior analyses (Bowden et al. 1985). In accordance with the hypotheses, the affects and behaviors measured included the constructs of depressed mood, motor retardation, anxiety, agitation, and hostility. Validation of the hypotheses would occur if decreases in MHPG were correlated with changes in anxiety, agita-

Table 3. Relationships[a] between Changes in CSF Amine Metabolites and Behaviors in Depressed Patient Sample after 2½ Weeks of Treatment with Imipramine or Amitriptyline

	Responders (n = 29–35)			Nonresponders (n = 15–19)		
State Constructs	**MHPG**	**5-HIAA**	**HVA**	**MHPG**	**5-HIAA**	**HVA**
Anxiety	−0.13	0.40[b]	0.38[b]	–	−0.08	0.03
Hostility	−0.47[c]	0.00	0.23	−0.23	–	–
Motor retardation	0.47[c]	0.00	0.17	−0.35	–	–

[a] Pearson Product-Moment correlation.
[b] $p < .05$
[c] $p < .01$

tion, and motor retardation, and if decreases in 5-HIAA were correlated with changes in hostility and/or anxiety.

The order of analysis was first to examine the pattern of correlations in the total sample of depressed patients (i.e., both AMI and IMI treated; unipolar and bipolar patients; and responders, indeterminates, and nonresponders) to determine (a) if changes in the neurotransmitter systems and in the behaviors correlate; (b) the pattern of correlations of patients within that group who achieved recovery within four weeks of treatment (the responders). In order to identify relationships that were associated with the therapeutic actions of the drugs, the responder pattern was compared with that in the nonresponder group. Second, the patterns of correlations within the unipolar and bipolar subgroups were examined. Analyses using the total and the responders only, would be conducted in each subtype separately, because as already noted, these types had been previously found to differ in behavior and baseline biochemistry. Third, the differences in biochemical–behavioral relationships between the unipolar and bipolar samples, if any, were analyzed by comparing their patterns and specific relationships during treatment, through the utilization of the z test of the significance of difference between correlations (Edwards 1950).

RESULTS

Relationships of Drug-Induced Changes in CSF Concentrations of Neurotransmitter Metabolites and Behavior in the Depressed Patient Sample:

1. Total sample (unipolar and bipolar responders, indeterminates, and nonresponders; AMI or IMI treated): There were no significant correlations between percentage decreases in each of the three CSF metabolites (5-HIAA, MHPG, and HVA), and changes in any of the behavioral constructs for this group of patients (i.e., patients were included regardless of response type and treatment drug they received, at 2½ weeks of treatment).
2. Unipolar and bipolar patients, divided into responder and nonresponder types: When examining the total group of *responders* to the tricyclic drugs, the following relationships were found to be significant: (a) change in anxiety with change in the concentration of 5-HIAA, and with change in HVA; (b) change in motor retardation with change in the concentration of MHPG; (c) change in the level of hostility with change in the concentration of MHPG.

These relationships are presented in Table 3. The positive relationship between changes in 5-HIAA and anxiety indicates that the lesser the decrease in 5-HIAA, the greater the reduction in anxiety; the lesser the decrease in MHPG, the greater the reduction of motor retardation (see Discussion for a likely explanation for this seemingly paradoxical negative correlation). Conversely, the negative relationship of MHPG and hostility indicates that the greater the decrease in MHPG, the greater the reduction in hostility.

By contrast, in the nonresponder sample, no significant relationships of changes in the CSF metabolites with change in these behaviors were found (Table 3).

Relationships of Changes in CSF Metabolites and in Behaviors within the Subtypes of Depression

Unipolar Depressions:

1. Within this sample (IMI or AMI treated; responders, indeterminates, and nonresponders): changes in anxiety correlated with changes in the concentration of 5-HIAA (r = 0.33, $p < .05$, n = 37) and HVA (r = 0.36, $p < .05$, n = 36), such that the lesser the decrease in 5-HIAA and the lesser the increase in HVA, the greater the reduction in anxiety.

Table 4. Relationships[a] between Changes in CSF Amine Metabolites and Behaviors in Unipolar Depressives at 2½ Weeks of Treatment with Imipramine or Amitriptyline

	Responders (n = 17–21)			Nonresponders (n = 10–13)		
State Constructs	**MHPG**	**5-HIAA**	**HVA**	**MHPG**	**5-HIAA**	**HVA**
Anxiety	0.21	0.57[c]	0.42	–	−0.07	–
Hostility	−0.40	0.02	0.01	–	–	–
Motor retardation	0.54[b]	0.21	0.27	−0.33	–	–
Depressed mood	0.44	0.53[b]	0.32	−0.26	−0.23	–

[a] Pearson Product-Moment correlation.
[b] $p < .05$
[c] $p < .02$

2. Responder sample: (a) The change in 5-HIAA was correlated with the change in anxiety and with the change in depressed mood such that the increase of, or the less the decrease in 5-HIAA, the greater the reductions in anxiety and depressed mood (Table 4, Figure 1). These correlations were absent or in the opposite direction in the nonresponder group. (b) The change in MHPG was correlated with the changes in motor retardation (Figure 2), and at a borderline level with depressed mood ($p < .10$), such that the lesser the decrease in MHPG, the greater the reductions in motor retardation and depressed mood. In the nonresponder group, these correlations were nonsignificant (Table 4).

Bipolar Depressions:

1. Total sample (includes AMI and IMI treated; responders, indeterminates, and nonresponders). The greater the change in 5-HIAA, the greater the changes in anxiety ($r = -0.48$, $p < .05$, $n = 23$), and in depressed mood ($r = -0.45$, $p < .05$, $n = 23$), such that the greater the decrease in 5-HIAA, the greater the reductions in anxiety and in depressed mood.
2. Responder sample: (a) The greater the decrease in 5-HIAA, the greater the reduction in depressed mood (Table 5, Figure 3). (b) The lesser the decrease in MHPG, the greater the reduction in motor retardation (Figure 4). (c) The greater the increase in HVA, the greater the reduction in hostility.

The nonresponder sample was inadequate for correlational analyses. The multiple regression analyses of the data from the total sample and from the unipolar and bipolar subsamples did not add any information to the correlational results; therefore, only the bivariate analyses are reported.

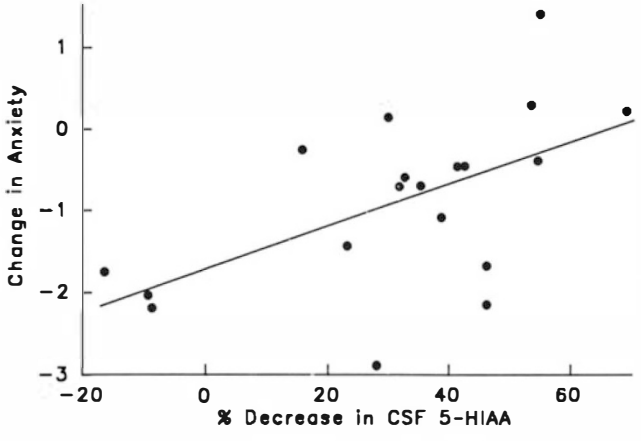

Figure 1. Unipolar treatment responders: Correlation of change from baseline in CSF concentration of 5-HIAA, and change in anxiety at 2½ weeks of tricyclic drugs.

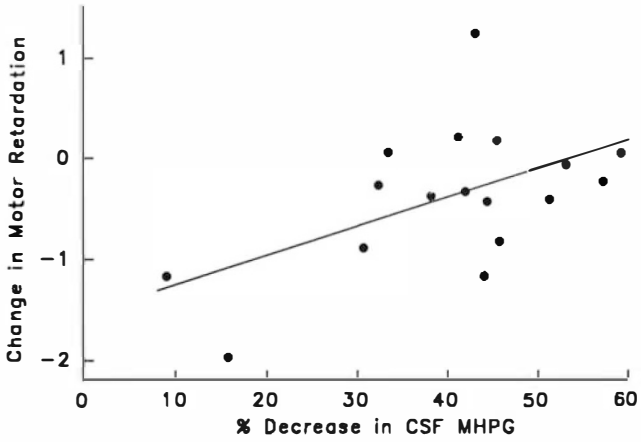

Figure 2. Unipolar treatment responders: Correlation of change from baseline in CSF concentration of MHPG, and change in motor retardation at 2½ weeks of tricyclic drugs.

Table 5. Relationships[a] between Changes in CSF Amine Metabolites and Behaviors in Bipolar Depressives at 2½ Weeks of Treatment with Imipramine or Amitriptyline

	Responders (n = 13–15)			Nonresponders (n = 3–7)[b]		
State Constructs	**MHPG**	**5-HIAA**	**HVA**	**MHPG**	**5-HIAA**	**HVA**
Anxiety	−0.39	−0.34	0.09	–	–	–
Hostility	−0.26	−0.21	0.60[c]	–	–	–
Motor Retardation	0.56[c]	−0.31	0.05	–	–	–
Depressed Mood	−0.23	−0.65[d]	−0.24	–	–	–

[a] Pearson Product-Moment correlation.
[b] Too few cases for correlation analysis.
[c] $p < .05$
[d] $p < .02$

Comparison of Relationships within the Unipolar and Bipolar Samples

It is evident from Table 4 and Table 5 that although one of the key relationships is the same for unipolar and bipolar groups, the patterns of relationships within the two subtypes are different. Specific findings are:

1. For the bipolar sample, the decrease in 5-HIAA in the bipolars was directly correlated with the reduction in anxiety and depressed mood; in the unipolar group, in contrast, the lesser the decrease in 5-HIAA, the greater the reduction in anxiety. These relationships were primarily due to the treatment responders within both groups.
2. Within the responder groups, subtype differences were present. Whereas reductions in 5-HIAA concentrations were correlated with reductions in depressed mood in bipolars, the lesser the decreases of 5-HIAA in unipolars, the greater the reductions in anxiety and depressed mood. The correlation between reduction in 5-HIAA and depressed mood was 0.54 in unipolar and −0.65 in bipolar depressed patients; the correlation of the reduction in anxiety with the decrease in 5-HIAA in unipolar patients was 0.57 and in bipolars was −0.34. These correlations were in the opposite direction and differed significantly from each other [z test, $p < .05$ Edwards (1950)].
3. In both the unipolar and bipolar samples, the lesser the decrease in MHPG, the greater the reduction in motor retardation.

DISCUSSION

To summarize, the following are conclusions:

1. Drug-induced changes in the functioning of the

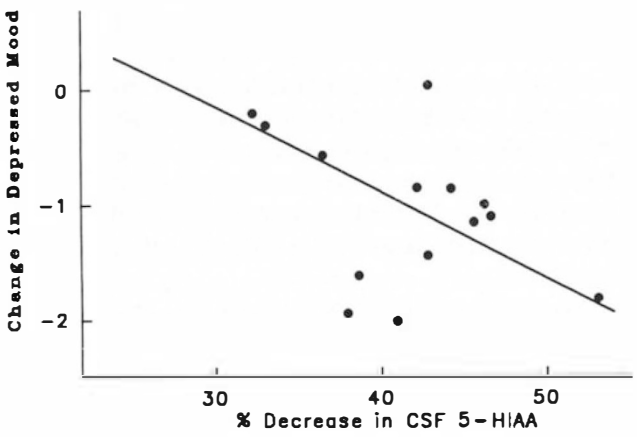

Figure 3. Bipolar treatment responders: Correlation of change form baseline in CSF concentration of 5-HIAA, and change in depressed mood at 2½ weeks of tricyclic drugs.

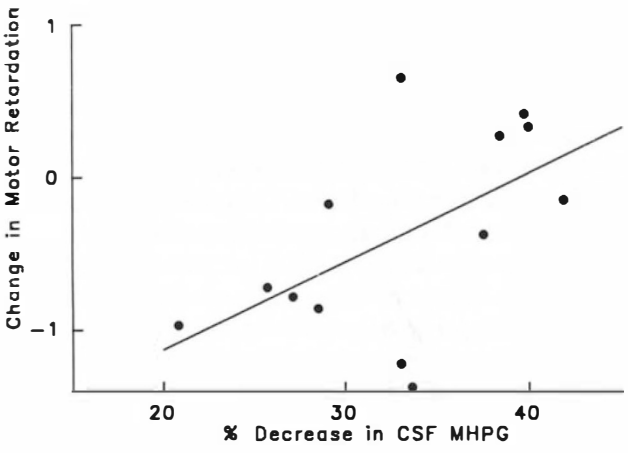

Figure 4. Bipolar treatment responders: Correlation of change from baseline in CSF concentration of MHPG, and change in motor retardation at 2½ weeks of tricyclic drugs.

Table 6. Unipolar and Bipolar Responders: Comparison of Correlations of Drug-Induced Change in 5-HIAA and MHPG with Changes in Mood and Behavior

	Relationships		
Responder Sample	5-HIAA and Anxiety	5-HIAA and Depressed Mood	MHPG and Motor Retardation
Unipolar	0.57[a,c]	0.53[a,c]	0.54[a]
Bipolar	−0.34	−0.65[b]	0.56[a]

Significance of r: [a] $p < 0.05$; [b] $p < 0.01$; [c] unipolar r significantly different than bipolar r, $p < 0.05$.

5-HT, NE, and dopamine systems in severely depressed patients (as reflected in changes in the concentrations of their major metabolites in CSF), were associated with changes in various behavioral components of the disorder. This was evident when patients were separated into unipolar and bipolar, and responder and nonresponder groups.

2. Changes in NE and 5-HT systems were associated differently with the various behaviors and emotions.
3. Changes in the NE system were found to be associated with changes in the motor retardation component of the depressive state in both unipolar and bipolar patients, but only in treatment responders. There was a borderline association of the change in depressed mood with the change in CSF MHPG, but only in the unipolar responders.
4. Changes in the 5-HT system were associated with changes in the level of anxiety in both unipolar and bipolar subtypes.
5. Changes in the 5-HT system in the responders were associated with changes in depressed mood in the unipolar and bipolar patients, and with changes in anxiety in the unipolars. These associations were not found in the nonresponders.
6. The direction of the associations of MHPG concentrations and the motor retardation component were the same for the unipolar and bipolar subtypes (i.e., although most responders showed a decrease in motor retardation, the lesser the decrease in MHPG, the greater the reduction in motor retardation).
7. The directions of the significant associations for 5-HIAA and anxiety were opposite in the unipolar and bipolar groups. For the unipolar responders, the lesser the decrease in 5-HIAA, the greater the reductions in anxiety and depressed mood; for the bipolar responders, the greater the decrease in 5-HIAA concentration, the greater the reduction in depressed mood.
8. The greater decrease in HVA in tricyclic drug responders, the greater the decrease in anxiety. The greater the decrease of HVA in bipolar responders, the greater the reduction in hostility.

Despite the cumulative evidence that NE and 5-HT systems are associated with the therapeutic action of the tricyclic drugs (Maas et al. 1991), it has not been demonstrated that changes in the functioning of these systems play a role in causing recovery in depressed patients (i.e., the same biochemical changes appear to occur in both patients who respond and who do not respond to treatment) (Bowden et al. 1985). In this study, the roles of these neurotransmitter systems were measured through their associations with changes in specific components of the depressive disorder (anxiety, depressed mood, hostility, and psychomotor activation), rather than changes in the global depressive disorder. This approach demonstrated clear associations between biochemical and behavioral changes in patients who responded to treatment.

Differing Behavioral Relationships of the NE and 5-HT Systems

We had previously found that the first facets to change during the process of recovery with these drugs were the levels of anxiety and hostility (Katz et al. 1991). The findings that certain behavioral components were associated directly with the NE and 5-HT systems were suggested by Carlsson et al. (1969) supporting the observations of Kielholz (1968) that the drugs had multiple actions on the depressive disorder. The association of the NE system with the psychomotor component was supported by our results for depression (Redmond et al. 1986) and in this study's sample of manic patients (Swann et al. 1987). Although the association of the 5-HIAA concentration in CSF with the mood aspects of the disorder was hypothesized earlier by investigators, the current findings identify a somewhat stronger relationship of the 5-HT system with anxiety than with depressed mood. The presumption of a stronger link of 5-HT with anxiety is based on the earlier finding that the change in anxiety appears to precede the change in depressed mood in the sequence of drug-induced behavioral and mood changes (Katz et al. 1987), and in this study's finding that changes in CSF 5-HIAA were related to changes in anxiety in both bipolar and unipolar patients.

It is useful at this point to recall that at 2½ weeks of treatment, the drug responders had changed significantly on most facets of the depressive disorder. At this time, therefore, it is more difficult to detect differential changes among the behavior variables and their specific relationships with neurotransmitter variables.

Because the inverse correlation in treatment responders between the drug-induced change in MHPG

and the motor retardation component of the depressed state was not expected and is difficult to explain, we examined the relationship of change in MHPG to the baseline MHPG level. The correlation was quite significant ($r = 0.68$, $p < .01$), indicating that those patients with a smaller percentage of change also had lower baseline values of MHPG. We then compared the patients with the upper third of baseline values of MHPG (range: 51 pmol/ml to 70 pmol/ml) with the group having the lower third of values (range: 26.9 to 41 pmol/ml) with regard to their 2½ week treatment MHPG values and their improvement on motor retardation. The posttreatment MHPG mean value for the lower baseline group was 23.9 pmol/ml, for the higher baseline group, 29.9 (indicating that both groups were apparently moving toward the same endpoint). The amount of improvement on motor retardation was, as noted, greater for the lower baseline MHPG group than for the higher baseline group. Even though motor retardation does not show significant improvement until two or three weeks of treatment (Katz et al. 1987), it appears that the lower baseline MHPG group was improving more rapidly than the high baseline group. The inverse correlation between drug-induced changes in MHPG and motor retardation is therefore somewhat misleading in that despite the lower baseline MHPG group showing a smaller percentage of change, they actually decreased to a lower posttreatment MHPG value than did the high baseline group. The finding, therefore, indicates that within treatment responders, a relatively low baseline CSF MHPG value (although subject to a lesser percentage change with treatment than a high baseline value) is associated with greater improvement on motor retardation.

This result is consistent with an earlier finding that for bipolar patients a lower baseline urinary or CSF MHPG in the depressed sample was associated with a favorable clinical response to tricyclic drugs (Maas et al. 1984). That general clinical finding can now be further specified as follows: although most patients responsive to tricyclic drugs will improve on motor retardation and depressed mood within 2½ weeks, those with a low baseline CSF MHPG will improve more rapidly than those patients with a higher baseline MHPG, despite the latter group having a proportionately greater decrease in MHPG. The finding provides evidence that supports low MHPG in CSF as a "marker" in depression (primarily in bipolar patients) for response to tricyclic drugs and that within treatment responders, it is associated with more rapid improvement in motor retardation.

The nature of the associations of neurotransmitter and behavioral changes would be more clearly defined if these relationships could have been examined earlier in treatment (i.e., within the first seven to ten days, when differences in effects across the various behaviors in the responders were clearly present). Nevertheless, resolution from this analysis is evident at 2½ weeks among the various relationships, and certain significant associations appear to be consistent with earlier research. The changes in the NE system were correlated more highly with the psychomotor component of the depressive state, secondarily with mood. By contrast for the 5-HT system, the changes were primarily associated with mood aspects, notably anxiety, and depressed mood. The findings reinforce that these neurotransmitter systems, although partially overlapping in their functioning, are associated with the expression or regulation of a different pattern of behaviors and emotions.

Differences between the Patterns of Relationships within the Unipolar and Bipolar Subtypes

Although change in MHPG correlated with change in motor retardation of the treatment responders, the relationship between 5-HIAA and anxiety and/or depressed mood was an inverse one in the unipolars and in the positive direction for the bipolars.

There is controversy about whether the decrease of 5-HIAA in CSF to a level significantly below that of healthy controls (Koslow et al. 1983) is or is not a reflection of an enhancement in 5-HT transmission in the brain (Eriksson and Humble 1990; Meltzer 1990). If the decrease in 5-HIAA is a reflection of enhanced transmission within the 5-HT system, than its association with the reductions in depressed mood and anxiety in bipolar depressions (along with the associated improvement in motor retardation) would explain in great part the therapeutic action of the tricyclic drugs in this form of the disorder. The inverse association of changes in 5-HIAA and anxiety in unipolars indicated that the smaller the decrease or an increase (Figure 1) of 5-HIAA, the more improvement in anxiety (baseline and change in CSF 5-HIAA unlike the case with MHPG, were not correlated). This suggests that the role of the 5-HT system is different in this form of depression, or irrelevant to the therapeutic action of the drug.

The level of anxiety is significantly higher in unipolar than in bipolar patients (Beigel and Murphy 1971; Katz et al. 1982), and it appears therefore, that as with the earlier findings of differences in their behavior and baseline chemistry, the biochemical changes induced by the drugs relate in different ways to behavior and emotions in the unipolar and bipolar subtypes. It provides additional evidence that the unipolar and bipolar types, despite their comparable rates of response to the drugs, represent different disorders. The practice in earlier research of merging these two subtypes of patients partly explains why results in small sample studies on these issues were often conflicting.

On Mechanisms of Action of Tricyclic Drugs

These results reinforce that the tricyclic drugs have multiple actions that are mediated through changes in the NE and 5-HT systems and through ways that are presently unknown.

In light of the association of changes in the 5-HT system with changes in aspects of mood, notably anxiety (the common aspect of most psychopathologic states) and depressed mood, the new selective 5-HT antidepressants would be expected to find applications for other mental disorders. The 5-HT drugs have been found to be effective for specific anxiety states (Deakin et al. 1991) similarly to the tricyclics, and in addition, for obsessive–compulsive states (Insel 1991) where anxiety is presumed a major role in the disorder and psychomotor disturbance (more highly associated with the functioning of the NE system), a lesser role.

Because of the complexity of the ways these neurotransmitter systems interact (Potter et al. 1989; Maas et al. 1991) and the different nature of their relationships with behavior, it is evident that to uncover the specificity of each neurotransmitter system, future studies must apply more refined behavioral measures. In particular, the manner in which the new targeted drugs affect these neurochemical–behavioral interactions in different disorders needs to be examined at several timepoints during treatment.

To uncover the relationships between drug-induced changes in brain biochemistry and specific changes in behavior in the unipolar and bipolar forms of depression will also require measures of brain neurotransmitter functioning that are more direct and clearly interpretable. This study utilized indirect or secondary measures of brain neurotransmitter functioning. To the extent that more direct measures of brain neural transmission (e.g., positron emission topography, in vivo measures of receptor activity) can be used in conjunction with refined measures of behavior, applied sequentially during treatment, we should obtain even clearer information regarding the mechanisms of antidepressant drug action.

In conclusion:

1. Drug-induced changes in 5-HT and NE systems were directly related to changes in critical behavioral and emotional components of the depressive disorder, but not to the disorder as a whole.
2. NE and 5-HT systems appear to relate differently to these behavioral facets (i.e., the NE system more consistently with the psychomotor component of the depressed state than with mood aspects, whereas the 5-HT system is more related to the mood aspects of the disorder, notably anxiety and depressed mood).
3. During treatment, these affect and motor components appear to change at different rates reflecting the multiple actions of the tricyclic drugs. In severe depression, anxiety and agitation in one respect, and depressed mood and retardation in another, reflect opposed states of arousal that appear to be equally focal to the disorder. They therefore, can represent separate targets for treatment, as can hostility, which also is a critical facet of the depressed state.
4. In accordance with differences in the baseline biochemistry and behavior of the unipolar and bipolar subtypes, the drug-induced changes in their biochemistry related differently to behavioral changes in the two subtypes. This provided further evidence that the unipolar and bipolar types represent different disorders.
5. The relationships of baseline and the amount of change in the NE system to the psychomotor component of the depressive disorder was the same in the unipolar and bipolar subtypes. This finding in treatment responders in addition to the earlier finding, that a lower concentration of MHPG in CSF is associated with a positive response to tricyclic drugs provides further evidence that baseline MHPG level is a marker for response to antidepressants.
6. The relationships of the mood aspects to change in the 5-HT system were different in the two subtypes, suggesting that the biochemical and behavioral differences between the unipolar and bipolar disorders are linked to the functioning of the 5-HT system.

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