ORIGINAL ARTICLE

Transient Depressive Relapse Induced by Catecholamine Depletion

Potential Phenotypic Vulnerability Marker?

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Background: Although state-related alterations in catecholamine function have been well-described in depressed subjects, enduring abnormalities have been less reliably identified. In our study, medication-free subjects with fully remitted major depression underwent a paradigm of catecholamine depletion, via use of the tyrosine hydroxylase inhibitor α-methylparatyrosine.

Method: Subjects underwent 2 sets of testing conditions in a double-blind, random-ordered, crossover design, approximately 1 week apart. They underwent active catecholamine depletion (via oral administration of 5 g α-methylparatyrosine) or sedation-controlled, sham catecholamine depletion (via oral administration of 250 mg diphenhydramine hydrochloride), during a 2-day observation. Serial mood ratings and blood samples were obtained.

Results: Fourteen subjects completed the active testing condition; 13 completed sham testing. Subjects experienced marked, transient increases in core depressive and anxiety symptoms, as demonstrated by a mean 21-point increase on Hamilton Depression Rating Scale scores. Furthermore, 10 (71%) of 14 subjects fulfilled relapse criteria during active testing, whereas 1 (8%) of 13 subjects did so during sham testing. The severity of the depressive reaction correlated with baseline plasma cortisol levels ($r = 0.59$; $P = .04$).

Conclusions: Euthymic, medication-free subjects with a history of major depression demonstrate significant depressive symptoms when undergoing testing with α-methylparatyrosine. This depressive reaction may represent a reliable marker for a history of depression. Further work is needed to clarify the significance of this finding.

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DURING THE past 3 decades, intensive research effort has focused on the pathophysiological features of major depression and the mechanism of action of treatments. Initial observations in this endeavor generated the catecholamine hypotheses,[1-5] which proposed "that some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain."[4] Although this hypothesis has proven limited in explaining newer findings,[6,7] the landmark observations on which it is based remain timely and provocative, meriting renewed research interest. These observations included the following naturalistic challenges: antihypertensive medications that inhibit catecholamine synthesis (α-methylparatyrosine[8,9]) deplete neuronal catecholamine stores (methyldopa) or deplete monoamine content (reserpine) robustly affect mood in a subset of vulnerable patients who are treated with these medications. Methyldopa[10-13] and reserpine[8,9,14] were commonly associated with the emergence of clinically significant depressive symptoms in patients who had histories of clinical depression.[14] These depressions occurred within days to months after initiation of antihypertensive therapy and were often severe enough to warrant hospitalizaion.

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Since these studies were completed before maintenance pharmacotherapy was standard practice, the cited findings suggest that medication-free subjects with a psychiatric history of major depression

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PATIENTS AND METHODS

PATIENTS

Sixteen medication-free, euthymic, previously depressed subjects in clinical remission for at least 3 months were recruited from the community at large via paid advertising. One subject was disqualified after evidence of protocol violation, 2 subjects completed only active testing, and 1 subject completed only sham testing. They all gave written informed consent to participate in a research study on the behavioral effects of α-methylparatyrosine and diphenhydramine hydrochloride administration. The subjects were informed that the study challenge might lead to significant mood changes, possibly causing a return of their depressive symptoms. The study was approved by the institutional reveiw boards of the West Haven Veterans Affairs Medical Center and Yale University, New Haven, Conn.

Based on open-ended clinical interviews, the Structured Clinical Interview for *DSM-III-R*, and the Yale Depression Inventory,[25] diagnoses were made by consensus of 2 of 4 research psychiatrists (R.M.B., M.N., H.L.M., A.A). Each patient met *DSM-III-R* criteria[26] for major depression in remission. Baseline 25-item Hamilton Depression Rating Scale (HDRS) scores were less than 10 points. Subjects were not currently taking over-the-counter or prescription medications. They denied histories of illicit substance use and did not meet criteria for alcohol or substance abuse diagnoses, as confirmed by results of daily urine toxicology screening. Subjects had no major medical illnesses, as confirmed by results of a physical examination, laboratory tests (electrolyte levels, complete blood cell count, liver and thyroid function tests, and thyroid stimulating hormone level), and electrocardiography. Female subjects of child-bearing potential had negative results of serum β-human chorionic gonadotropin testing. Patient demographics are noted in **Table 1**.

METHODS

Subjects underwent active (α-methylparatyrosine, five 1-g doses administered orally during 28 hours) and sham catecholamine depletion challenges (diphenhydramine hydrochloride, five 50-mg doses administered similarly) in a random-ordered, double-blind, crossover design, under previously described conditions.[15-18] Both study conditions were performed 1 to 2 weeks apart. Eight of the 15 subjects were assigned to undergo α-methylparatyrosine testing first. Diphenhydramine is used as an active control agent to approximate the level of sedation induced by α-methylparatyrosine.[15-17]

Each study condition involved 4 days, performed on an outpatient basis at the Biostudies Challenge Unit of the West Haven Veterans Affairs Medical Center. Behavioral ratings and blood samples for monoamine metabolite and hormone level screenings were obtained daily (8:00 to 9:00 AM and 3:00 to 4:00 PM) during days 2 and 3 and once in the mornings of days 1 and 4. Medication capsules containing α-methylparatyrosine (1 g) or diphenhydramine hydrochoride (50 mg) were given during day 2 (9:00 AM; noon; and 7:00 PM) and day 3 (9:00 AM and noon). Vital signs were assessed thrice daily. Daily urinalysis was performed to allow for early detection of the potential, but unlikely, complication of urinary crystal formation.[27] To minimize this related risk, subjects drank at least 2 L water during each medication day. For subjects who described a nadir of mood occurring after returning home on the second medication day, an additional set of behavioral ratings were retrospectively obtained on the morning of the last study day. Patients' clinical status was assessed each day before discharge from the challenge unit. Because of expected sedation, subjects were not allowed to drive themselves after testing days.

Behavioral ratings included the modified HDRS with the weight change subitem omitted,[25] the Side-Effects Checklist (SECL),[28] and the Inventory of Depressive Symptoms (IDS). The SECL questionnaire assesses the presence of physical symptoms on an ordinal scale (ie, not at all, mild, moderate, or severe).

BIOCHEMICAL ASSAYS

Serum samples of 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) and homovanillic acid (HVA) levels were stored at −70°C and assayed in batch with previously described methods that use gas chromatography and mass spectrometry, with deuterated internal standards.[29,30] Plasma cortisol levels were analyzed as described previously, via an iodine 125 radioimmunoassay kit (Incstar Corp, Stillwater, Minn) with use of standards.

DATA ANALYSIS

The primary hypothesis, that subjects experience a greater depressive reaction undergoing active compared with sham catecholamine depletion, was assessed by use of continuous (eg, HDRS scores) and categorical outcome variables (eg, relapse). First, paired *t* tests of HDRS scores assessed baseline and change (ie, peak HDRS score minus baseline HDRS score [ΔHDRS]) differences between testing conditions. Baseline measures were from the morning measures on study day 2. Peak measures were the maximum measures from day 3. Similar analyses were performed for secondary analyses (ie, IDS and each item of the SECL and HDRS). Fisher exact tests were used to assess the categorical outcomes. The relapse category, as defined previously,[17,31] signified a 50% increase in the HDRS score and a peak score of at least 17 points.

To assess monoamine metabolite changes, paired *t* tests were performed, with the second time point defined as the minima of day 2. To determine correlates of α-methylparatyrosine–induced mood changes (ie, ΔHDRS), baseline demographic characteristics, monoamine metabolite levels, and plasma cortisol levels were assessed via Kendall τ or Pearson correlations. Unless otherwise indicated, data are given as mean ± SD.

may be vulnerable to depression induced by catecholamine-depleting medications. If so, depressive reactions in response to catecholamine depletion may represent a phenotypic trait marker for depression.

A method of catecholamine depletion via α-methylparatyrosine administration has been developed and validated by our group and others. Catecholaminergic function may be significantly altered by 2-day administration

Table 1. Demographic Characteristics*

Patient No./Sex/ Age, y/Race	Diagnosis (Confirmed by SCID) and Clinical Attributes†	No. of Depressive Episodes	Duration of Latest Episode, mo	Duration of Remission Before Study, mo	Lifetime No. of Antidepressant Trials	Lifetime Medication History‡	Time Without Medication Before Study, mo
1/F/46/W	r, m	≥5	2	13	2	TCA, MAOI, S	9
2/F/42/W§	a, r	≥5	3	14	1	S	10
3/F/38/W	r	≥5	29	13	1	S	21
4/M/36/W	r	≥5	7	52	0	None	NA
5/F/28/H	r	2	20	14	2	TCA, S	30
6/F/45/W	r, D	≥5	1	11	1	TCA	15
7/M/25/W	r	3	13	46	3	S	39
8/M/33/W	r, a	3	3	7	2	S	6
9/F/19/W	s, a	1	6.5	8	1	S	3
10/F/30/W‖	r	2	5	5	1	S	10
11/F/20/W	s, a	1†	12	4	1	S	8
12/M/37/W	r, m	3	10	9	2	S	16
13/M/20/W§	r, GAD	2	6	18	1	S	13
14/F/20/W	r	3	7	12	2	S	12
15/F/37/W	r	4	9	48	0	None	NA
Mean ± SEM	. . .	3#	8.9 ± 1.9	18.3 ± 4.2	1.3 ± 0.2	. . .	14.8 ± 2.8

**SCID indicates Structured Clinical Interview for* DSM-III-R*; W, white; r, recurrent episodes; m, melancholic episodes; TCA, tricyclic antidepressant drug; MAOI, monoamine oxidase inhibitor antidepressant drug; S, selective serotonin reuptake inhibitor antidepressant drug; a, atypical episodes; NA, not applicable, as subjects never received medications; H, Hispanic; D, dysthymia; s, single episodes; GAD, generalized anxiety disorder; and ellipses, not applicable.*

†All subjects met criteria for major depressive episode in remission. Subjects 1, 5, and 11 reported a remote history of 1 suicide attempt during a depressive episode. Subject 7 had a history of anorexia and obsessive-compulsive disorder, currently in remission. Subject 11 had a history of anorexia nervosa and bulimia nervosa, currently in remission. In addition, subject 11 had 3 previous episodes of major depressive disorder not otherwise specified.

‡For all subjects who had lifetime medication trials, the most recent trial was a selective serotonin reuptake inhibitor with the exception of subject 6. Subject 3 reported a medication history that included a paroxetine trial of less than 6 weeks.

§Subject completed only active testing.

‖Subject completed only control testing.

#Indicates median number.

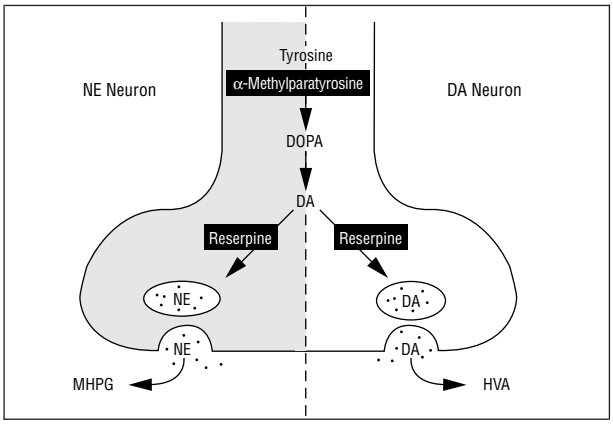

Figure 1. *The synthesis of catecholamines is depicted schematically, with the shaded area denoting norepinephrine (NE) neurons and the unshaded area denoting dopamine (DA) neurons. The synthetic pathway shared by both neurons is shown overlapping both areas. The amino acid tyrosine is actively transported into the cytoplasm and is converted to dihydroxyphenylalanine (DOPA) via enzymatic reaction with tyrosine hydroxylase (TH). This rate-limiting step in catecholamine synthesis may be blocked by α-methylparatyrosine, a TH inhibitor. The α-methylparatyrosine presumably diminishes production of DOPA and ultimately may result in diminished synaptic release of catecholamine neurotransmitters in human subjects. The DOPA is converted to DA via L-aromatic amino acid decarboxylase. In noradrenergic neurons, DA subsequently is stored in granules and is converted by DA-α-hydroxylase to NE. This storage process in catecholamine neurons is disrupted by reserpine. Synaptic enzymes metabolize NE and DA to 3-methoxy-4-hydroxyphenyl-ethyleneglycol (MHPG) or homovanillic acid (HVA), respectively.*

of oral α-methylparatyrosine, an inhibitor of tyrosine hydroxylase (TH), the rate-limiting enzyme in the synthesis of catecholamines (**Figure 1**). Under conditions similar to these, catecholamine metabolite levels are markedly reduced in samples of urine,[8] plasma,[15-18] and cerebrospinal fluid (CSF).[19] Furthermore, findings of markedly enhanced serum prolactin levels[20] and markedly diminished nocturnal melatonin secretion[21] suggest α-methylparatyrosine administration results in a functional disruption of catecholaminergic neurotransmission. Blood monoamine metabolite levels normalize within 4 days of discontinuing α-methylparatyrosine therapy.[8] Disruption of catecholamine function via use of α-methylparatyrosine[8] has been described in approximately 90 control subjects to date, without significant mood alteration.[18,22,23]

The purpose of our investigation is to determine if rapid reduction in the levels of the brain catecholamines, noradrenaline and dopamine, induces a depressive reaction in medication-free, euthymic subjects who have a history of major depression. Catecholamine depletion is achieved by the use of α-methylparatyrosine. Furthermore, given that vulnerability to clinical relapse after successful treatment correlates with abnormal hypothalamic pituitary axis function,[24] plasma cortisol levels were assessed serially during the study. We predicted that the depletion challenge in our study population would result in a depressive reaction.

RESULTS

PATIENT DISPOSITION

Sixteen subjects signed informed consent. One subject completed active testing conditions but was excluded because of protocol violation; he had been taking an unidentifiable anabolic steroid surreptitiously during the pre-

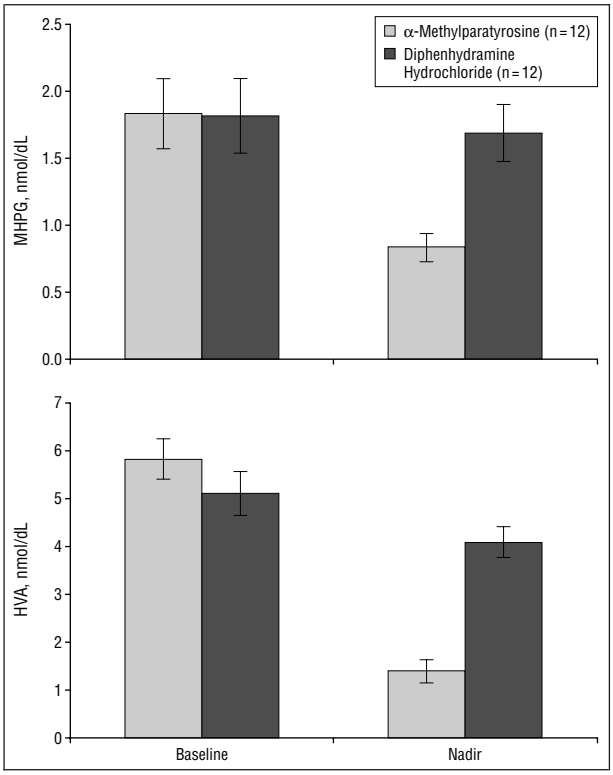

Figure 2. *Administration of α-methylparatyrosine was associated with marked reductions in levels of plasma 3-methoxy-4-hydroxy-phenylethyleneglycol (MHPG) (top) and homovanillic acid (HVA) (bottom). Baseline plasma levels were drawn on the second testing day before medication administration. Nadir plasma levels represent the lowest of the other sampled times during the 2-day medication administration. During active testing, MHPG and HVA levels decreased by 51% and 86%, respectively; whereas during sham testing, those levels decreased by 5% and 12%, respectively. Baseline scores did not differ by treatment condition for MHPG (paired* t *test,* P = *.61) and HVA levels (*P = *.56); however, decrements in MHPG (*P = *.002) and HVA metabolite levels did (*P = *.001). Data are given as mean ± SEM.*

vious month. After experiencing a marked mood change (ie, HDRS score rising from 9 to 37 points) during active testing, he volunteered this information. His data are not included in the analyses, tables, or figures. Two subjects discontinued the study after undergoing the active test condition, citing significant mood exacerbations (HDRS increases of 33 and 23 points). One subject discontinued after completing the sham test, for scheduling reasons (HDRS increase of 1 point). Subjects who did not complete both testing days were excluded from analyses. At the time of α-methylparatyrosine testing, all subjects had been in remission for at least 4 months and medication free for at least 3 months before testing.

α-METHYLPARATYROSINE–INDUCED CHANGES IN PLASMA MHPG AND HVA LEVELS

Consistent with previously published reports,[16-18] administration of α-methylparatyrosine reduced HVA and MHPG levels (**Figure 2**).

MOOD EFFECTS OF α-METHYLPARATYROSINE

Active testing conditions were associated with significantly greater changes in HDRS than sham testing

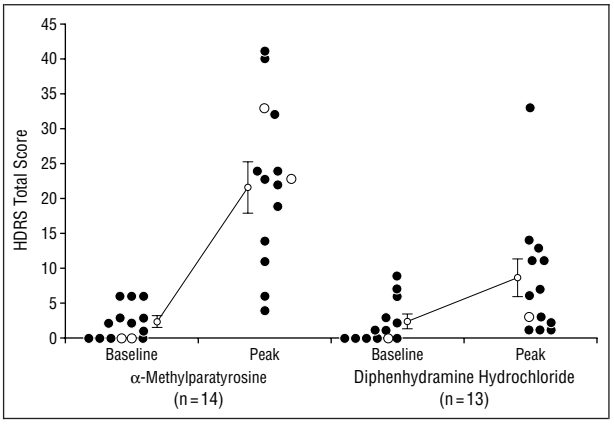

Figure 3. *Testing with α-methylparatyrosine was associated with marked increases in Hamilton Depression Rating Scale (HDRS) scores, whereas sham testing was not. Analysis of subjects completing both testing conditions (n = 12) revealed that baseline HDRS scores do not differ by treatment condition (*P>*.99); however, testing with α-methylparatyrosine, compared with diphenhydramine hydrochloride, significantly increases HDRS scores transiently (*P = *.007). Data are given as mean ± SEM. Open icons represent patients who completed only 1 testing condition (these data points were not included in analyses).*

(**Figure 3**). During active conditions, mean HDRS scores increased markedly (baseline, 3.1 ± 3.2; peak, 23.9 ± 12.0); whereas changes were less robust during sham testing (baseline, 2.8 ± 3.4; peak, 9.0 ± 9.7). Baseline HDRS scores did not differ between groups (paired *t* test, *P*>.99); ΔHDRS scores differed significantly (*P* = .007). Peak HDRS increases occurred invariably on day 2 of active drug administration, typically 3 to 10 hours after the last dose. Timing of HDRS increases during sham testing was less consistent. Similarly, IDS ratings robustly increased during active (baseline, 8.2 ± 7.2; peak, 23.6 ± 14.8) but not sham (baseline, 6.1 ± 6.6; peak, 10.0 ± 8.1) testing. Individual HDRS items were also assessed and reported without correction for multiple comparisons (**Table 2**). Analysis also revealed significant differences in peak minus baseline IDS scores (paired *t* test, *P* = .04); baseline values did not differ by testing condition (*P* = .49).

Ten (71%) of 14 subjects who underwent active α-methylparatyrosine testing experienced a depressive relapse, whereas 1 (8%) of 13 subjects who underwent sham depletion met similar criteria (Fisher exact test, *P* = .001).

The subjects who experienced a significant depressive reaction reported feeling near baseline on assessment at the follow-up (day 4) appointment. Mean HDRS scores on the follow-up day were similar for active (2.43 ± 3.32 points) and sham testing conditions (2.66 ± 3.07 points) (paired *t* test, *P* = .67). One subject who demonstrated marked anxiety symptoms reported persisting anxiety after 3 weeks, at which time a 25-item HDRS rating indicated that he was near his baseline score (ie, 9 points). During this period, he did not fulfill criteria for a major depressive episode. Distinguishing features of this patient include previous diagnosis of a generalized anxiety disorder, upcoming moderate stressors, and a family history of bipolar disorder in a first-degree relative. Given that short-term α-methylparatyrosine

Table 2. Mean Hamilton Depression Rating Scale (HDRS) Subitem Scores During Testing With α-Methylparatyrosine and Diphenhydramine*

	Mean ± SD Score				
	α-Methylparatyrosine		Diphenhydramine Hydrochloride		
HDRS Item	Baseline	Peak	Baseline	Peak	P†
Decreased concentration	0.08 ± 0.29	2.67 ± 0.78	0.08 ± 0.29	0.92 ± 1.31	.001
Loss of energy	0.17 ± 0.39	3.17 ± 0.72	0.25 ± 4.52	2.00 ± 1.13	.003
Psychic anxiety	0.33 ± 0.49	1.92 ± 1.44	0.42 ± 0.52	0.58 ± 0.79	.01
Agitation	0 ± 0	1.08 ± 1.17	0.08 ± 0.29	0.17 ± 0.39	.02
Appetite change	0 ± 0	1.17 ± 1.03	0.17 ± 0.39	0.33 ± 0.49	.02
Somatic anxiety	0 ± 0	1.50 ± 1.41	0 ± 0	0.33 ± 0.89	.02
Depressed mood	0.25 ± 0.45	2.33 ± 1.23	0.25 ± 0.45	1.23 ± 1.14	.03
Loss of interest	0.08 ± 0.29	2.50 ± 1.31	0.08 ± 0.29	1.08 ± 1.38	.04
Hopelessness	0.25 ± 0.45	1.67 ± 1.44	0.17 ± 0.39	0.58 ± 0.90	.09
Suicidality	0 ± 0	0.50 ± 1.00	0 ± 0	0 ± 0	.11
Worthlessness or failure	0.25 ± 0.45	1.50 ± 1.24	0.17 ± 0.39	0.58 ± 1.00	.13
Loss of sexual interest	0.08 ± 0.29	0.92 ± 0.90	0.08 ± 0.29	0.42 ± 0.67	.17
Helplessness	0.08 ± 0.29	1.50 ± 1.38	0.08 ± 0.29	0.75 ± 1.06	.26
Retardation	0.83 ± 0.29	0.92 ± 0.79	0 ± 0	0.50 ± 0.80	.27
Hypochondriasis	0.83 ± 0.29	0.67 ± 0.88	0 ± 0	0.33 ± 0.88	.28
Terminal insomnia	0.25 ± 0.62	0.42 ± 0.67	0.25 ± 0.45	0.33 ± 0.49	.28
Lack of insight	0 ± 0	0.80 ± 0.29	0 ± 0	0.17 ± 0.58	.34
Depersonalization	0 ± 0	0.80 ± 0.29	0 ± 0	0 ± 0	.34
Obsession or compulsions	0 ± 0	0.80 ± 0.29	0 ± 0	0.17 ± 0.58	.34
Middle insomnia	0 ± 0	0.50 ± 0.78	0.08 ± 0.29	0.50 ± 0.67	.64
Initial insomnia	0.17 ± 0.06	0.67 ± 0.89	0.17 ± 0.58	0.58 ± 0.90	.72
Pathologic guilt	0.08 ± 0.29	0.42 ± 0.52	0 ± 0	0.17 ± 0.58	>.99
Paranoia	0 ± 0	0 ± 0	0 ± 0	0 ± 0	>.99

*Data are from the 12 subjects completing both testing conditions. Data on the subitem, composite variable of diurnal variation not reported above.
†P values shown represent 2-tailed paired t tests on ΔHDRS (ie, peak minus baseline HDRS scores) between α-methylparatyrosine and diphenhydramine testing conditions, unadjusted for multiple comparisons. No baseline subitem scores statistically differed by testing condition.

administration has not been associated with the emergence of a major depressive episode[7,8,15-17,22,27,32] and the presence of significant stressors, it cannot be concluded that α-methylparatyrosine contributed to an enduring symptom exacerbation.

ASSESSMENT OF SIDE EFFECTS

Acute side effects of medication did not contribute to study discontinuation. Results of daily urinalysis revealed no cases of crystalluria. As detected by the SECL, α-methylparatyrosine administration was associated with greater increments in drowsiness than diphenhydramine administration ($P = .005$), although both groups manifested noticeable changes. Mean baseline to peak SECL scores of drowsiness during active and sham testing conditions were 1.7 ± 0.8 to 3.3 ± 0.9 and 1.8 ± 1.0 to 2.5 ± 1.1, respectively.

For the following 2 SECL items, effects nearly reached significance: difficulty sitting still ($P = .05$) and tremors or shakiness ($P = .05$). For the former item, mean baseline to peak scores for active and sham testing were 1.0 ± 0 to 1.6 ± 0.7 and 1.0 ± 0 to 1.2 ± 0.4, respectively; for the latter item, 1.0 ± 0 to 1.5 ± 0.9 and 1.0 ± 0 to 1.1 ± 0.3, respectively. Notably, patient 15 demonstrated severe bradykinesia and mild cogwheeling rigidity during active testing. These symptoms resolved within 1 day of medication discontinuation.

CORRELATES OF DEPRESSIVE REACTION

To determine possible factors related to the α-methylparatyrosine–induced depressive reaction, clinical and biological factors were analyzed for correlations with peak HDRS scores and change in HDRS scores. Clinical characteristics listed in Table 1 did not significantly correlate with α-methylparatyrosine–induced increases in HDRS scores ($P > .13$ for all comparisons). Duration of remission, analyzed categorically (ie, ≤12 vs >12 months), was not associated with significant differences in depressive reaction (20.4 ± 8.6 vs 23.0 ± 12.4, respectively; $P = .69$). Baseline, nadir, and percentage of drop in HVA or MHPG levels did not correlate with changes in HDRS scores. Importantly, history of medication treatment (ie, none vs any) did not correlate with depressive reaction. Two medication-free subjects demonstrated 10- and 37-point increases during active testing. Another patient with limited exposure to antidepressant medication (ie, <6 weeks of paroxetine) demonstrated a 12-point increase in HDRS scores during active testing. The small number of subjects who never received medication in our study limit conclusiveness of this observation. Similarly, lack of clinical and biological correlations may represent insufficient power. In addition, order effects on HDRS scores were not statistically significant ($P = .26$).

Baseline plasma cortisol levels correlated with severity of depressive reaction (ie, peak HDRS scores;

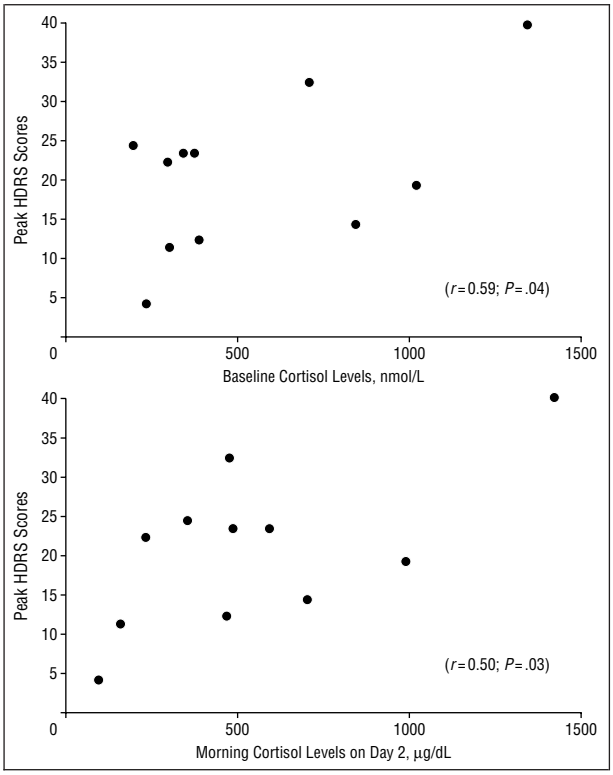

Figure 4. *Baseline (top) and morning of day 2 (bottom) plasma cortisol levels correlated with peak scores on Hamilton Depression Rating Scale (HDRS) during active testing with α-methylparatyrosine. Pearson correlation results are shown inset. Individual subjects are identified with unique icons that correspond to patient number as indicated in Table 1. Data were available for 11 of the 14 subjects completing active testing.*

$r = 0.59$; $P = .04$; n = 11) and nearly significantly correlated with HDRS score increases (ie, ΔHDRS scores; $r = 0.53$; $P = .09$; n = 11) (**Figure 4**). Plasma cortisol levels from the morning of day 2 correlated with severity of depressive reaction ($r = 0.65$; $P = .03$; n = 11) and HDRS score increase ($r = 0.62$; $P = .04$; n = 11). Cortisol, MHPG, and HVA levels were available for 11 of the 14 subjects completing active testing.

SUBJECTIVE EXPERIENCE

Impressionistically, 2 types of subjective patient experiences were described on open-ended interviews during the testing days. Commonly, patients reported that the induced reaction resembled their clinical depressive episode. Patient 3 reported on the second observation day "feeling sorry for myself," ruminating "What is wrong with me?" and a lack of interest in "doing anything." Patient 1 reported doing well until returning home on the evening of the second observation day, when she burst into tears, and

> I had an overwhelming sense of loss, an utter sense of loneliness, and a sense of failure. Everything seemed dark and dreary. I felt stuck in sadness. I felt like this is how I would feel from now on—this was it for life. This felt like the beginnings of a depression.

Patient 7 reported a

> . . . free floating sense of fear regarding anything that requires me to be active and functioning . . . like I lost the best part of myself . . . There was this feeling that I was able to do nothing but roll up into a ball. The only thing that gave me pleasure was to curl up into the fetal position. I didn't see a way to get out of it. I didn't think it would pass. I really thought the depression was back—that I was done for.

The HDRS scores for all 3 of these patients returned to baseline (0 or 1 point) within 24 hours of medication discontinuation.

In another common presentation, some patients, while reporting significant depressive symptoms, also described prominent symptoms of anxiety and/or irritability that did not typify their depressive episodes. Patient 14 described

> This mood—it came, it went, it came back again. It was trying to do stuff to me. I was in a struggle with my mood for control of myself. I kept crying. I was terrified these feelings would never go away.

She reported palpitations, a "pit" in her stomach, as well as general physical discomfort. Patient 6 became tearful and fidgety during the observation days, reporting a restlessness that was atypical of her previous depressions. During this time she described herself as feeling "trapped and stuck . . . vulnerable and lonely . . . a complete failure . . . my life is meaningless." Patient 15 became markedly irritable and fidgety. At one point she refused to answer questions. She reported

> . . . weakness throughout my body. I had a strange feeling in my legs, like a stiffness and numbness. I walked like a mental patient or someone with Parkinson's disease . . . There was a fear in my gut, like a primal fear. I was afraid of losing my legs, of no longer being able to walk . . . I began sweating.

All of these patients returned fully to baseline states within 1 to 2 days after the last medication dose.

COMMENT

Medication-free, euthymic subjects with a history of major depression differ significantly from never-depressed comparison subjects. In our study, subjects with a history of major depression in remission commonly demonstrated a clinically significant depressive reaction when undergoing α-methylparatyrosine administration (ie, 71% demonstrated a depressive relapse, and the mean HDRS score increase was 21 points), whereas the same subjects rarely demonstrated significant mood changes when undergoing control testing (ie, 8% demonstrated a depressive relapse, and the mean HDRS score increase was 6 points). In marked distinction, never-depressed healthy subjects without a family history of major depression in first-degree relatives demonstrated no significant mood changes under similar testing conditions with α-methylparatyrosine in previously reported studies.[18,23,32]

More than sham testing, α-methylparatyrosine testing evoked core symptoms of major depression, such as depressed mood, decreased concentration, loss of energy, psychic anxiety, agitation, appetite change, somatic anxiety, depressed mood, loss of interest, hopelessness, and worthlessness or failure. By subjective self-report, patients' experience of the active testing day was

commonly similar to their depressive episodes, but less intense.

RESULTS OF our study are in accord with those of limited reports on the use of α-methylparatyrosine in populations with a history of major depression. Among 52 patients with varied medical diagnoses who were treated with α-methylparatyrosine, 8 subjects experienced anxiety or agitated depression.[8] Of the 6 patients in that study with reported histories of psychic depression, 3 discontinued α-methylparatyrosine administration because of emerging agitation. The observed depressive reaction that is induced by catecholamine depletion may represent a phenotypic nonstate marker for major depression.

Several methodological considerations are warranted. First, diphenhydramine may not have preserved the study blind fully, in that α-methylparatyrosine testing was associated with higher levels of anergy and drowsiness than control testing, unlike what has been reported in previous studies.[15-17] Although this finding is consistent with the previous assertion that vulnerable subjects manifest a depressive reaction secondary to the sedative properties of α-methylparatyrosine,[7] peak levels of sedation preceded peak HDRS scores by at least 5 hours in 4 of the 10 subjects who experienced a depressive relapse. Furthermore, some subjects demonstrated substantial drowsiness during active testing without significant changes in HDRS scores, and increases in drowsiness did not correlate with HDRS score increases.

Our study design did not include a never-depressed control group for comparison. Nevertheless, previous studies on the behavioral effects of α-methylparatyrosine in such subjects have not revealed significant mood changes.[18,23,32] In a previous study examining never-depressed healthy subjects without a family history of depression, α-methylparatyrosine administration combined with active or sham tryptophan depletion resulted in no mood changes (ie, mean HDRS score increases of 2 points; range, 0- to 5-point increases).[18] These studies are comparable in that identical α-methylparatyrosine dosing was used, and that subject demographics were similar to those of our study (ie, age, 36.0 ± 12.5; 4 women and 4 men). McCann et al[23,32] administered α-methylparatyrosine (5.0-5.25 g during 33-40 hours) to a population of never-depressed men (mean age, 25 years; range, 21-39 years). Overall, mild and inconsistent anxiety and depressive effects were noted. Other studies using similar dosing of α-methylparatyrosine in never-depressed populations did not report worsening of mood, although mood rating scales were not used.[21,27] Other effects of α-methylparatyrosine on healthy subjects include increased anxiety in a few study subjects[23,33] and dystonia.[34]

By way of empirical characterization, the induced depressive reaction may represent a phenotypic nonstate marker for depression, a sequela of the depressive episode, a sequela of treatment, and/or a vulnerability marker for the development of future depressive episodes. The unlikelihood that the reaction is secondary to medication treatment is supported by observations of significant depressive reactions in subjects with limited or no past medication trials. The α-methylparatyrosine–induced depressive reaction does not represent a true trait finding, since actively depressed subjects who are medication free do not typically experience significant changes in their depressive symptoms[17]; however, results from a smaller sample contradict this finding.[19,35]

The results of our study are consonant with hypotheses of catecholaminergic dysfunction in depression. In support, postmortem studies of depressed suicide victims examining the locus ceruleus (LC) have revealed diminished density of noradrenergic transporter sites[36] and up-regulation of TH.[37] Conversely, all classes of antidepressant medications were found to reduce TH levels in the LC of rodents,[38] whereas stress and catecholamine-depleting agents increase TH levels.[39,40] Importantly, α-methylparatyrosine administration may mediate behavioral effects via disruption of dopaminergic function (as would be consistent with preclinical data) or may have physiologically important secondary effects that directly attribute to the behavioral findings. For example, catecholamine-depleting agents have been associated with alterations in LC firing rate,[40] neuropeptide Y levels,[41] corticotropin-releasing hormone (CRH) levels,[42] and acetylcholine levels.[43]

Conjecture on the mechanism of this α-methylparatyrosine–induced depressive reaction in medication-free, euthymic subjects with a history of major depression must involve consideration of putative trait abnormalities of the catecholaminergic system. Replicated trait findings include reduced tyramine sulfate conjugation following oral tyramine administration[44-46] and blunted growth hormone response to intravenous clonidine hydrochloride administration[47,48] in unipolar depressed subjects. The former finding has unclear pathophysiological significance.[44] The latter finding suggests that diminished postsynaptic α_2-adrenergic function may be a persistent abnormality in subjects with a history of major depression. Potentially, α-methylparatyrosine administration results in diminished noradrenergic output, hence diminishing postsynaptic α_2-adrenergic stimulation. In vulnerable subjects, with reduced postsynaptic α_2-adrenergic responsiveness, this further reduction may lead to depressive symptoms.

Despite the small sample size of our study, a correlation between baseline plasma cortisol levels and severity of the α-methylparatyrosine–induced depressive reaction was observed ($P = .59$ and $P = .04$, respectively). Subjects with higher baseline cortisol levels were proportionately more dependent on intact catecholamine function for maintaining a euthymic state. This finding is consistent with a mixed literature suggesting that abnormalities of cortisol regulation (ie, higher levels after dexamethasone administration) may correlate with higher basal levels of MHPG.[49] Furthermore, such persistent dexamethasone nonsuppression in treatment responders is associated with a vulnerability to relapse,[24] as may be persistent elevated CSF levels of CRH.[50] Speculation on the mechanism of this correlation based on observations of plasma cortisol levels would be premature and would be furthered by assessment of dexamethasone sup-

pression and CSF levels of CRH. Further caution is warranted in interpreting the above correlation, since the baseline plasma cortisol levels were impressionably high in several patients.

Previous work with nonhuman primates bears resemblance to our findings. Administration of α-methylparatyrosine has been associated with depressive-like syndrome in primates[51]; however, these symptoms may be attributed to sedation. Also, monkeys with early-life (ie, deprived of maternal rearing) and current stressors (ie, social isolation) may demonstrate depressive symptoms (ie, increased huddling and decreased locomotor activity).[52,53] Rhesus monkeys with such early and ongoing stressors demonstrate these behaviors when administered markedly lower doses of α-methylparatyrosine than their nonstressed counterparts, at doses not associated with acute sedation.[53] Furthermore, bonnet macaques reared under variable foraging stressors have been shown to have a blunted growth hormone response to clonidine,[54] as well as increased CSF levels of CRH,[55] with both findings correlating with each other.[56] Although extension of these results to human affective disorders may be premature, the results suggest that CRH–hypothalamic-pituitary-adrenal axis function—which may in turn be profoundly affected by early and current life stressors—may interact with postsynaptic α_2-adrenergic function in mediating vulnerability and expression of depression.[57] In testing this assertion in humans, clinical (eg, stressors) and neurobiological correlates of the α-methylparatyrosine–induced depressive reaction (eg, CRH levels and hypothalamic-pituitary axis responsiveness) need to be determined in our study population.

CONCLUSIONS

Our principal finding underscores and extends the founding observations of the original catecholamine hypothesis of major depression. Although the compelling phenotypic similarities of the α-methylparatyrosine–induced depressive reaction to clinical depression suggest similar pathophysiological mechanisms, the empirical and clinical significance of this finding requires further work. The direct, acute effects of α-methylparatyrosine (ie, reducing catecholamine synthesis) do not serve as an effective working model of the pathophysiological features of major depression. Nevertheless, our findings suggest that catecholamine function may play a crucial role in mood regulation for subjects who are vulnerable to depression. In so doing, catecholamine systems may directly affect the neuroanatomic substrate responsible for mood regulation or indirectly affect mood via interactions with multiple neuronal systems (eg, extrahypothalamic CRH or neuropeptide Y). Elucidation of the neurochemical, anatomic, and clinical correlates of α-methylparatyrosine–induced depressive reactions may further the understanding of pathophysiological processes involved in clinical depression. As a potential phenotypic nonstate marker, α-methylparatyrosine testing may represent a useful tool to study the genetics of unipolar depression.

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