Probing Brain Reward System Function in Major Depressive Disorder

Altered Response to Dextroamphetamine

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Background: The state of the brain reward system in major depressive disorder was assessed with dextroamphetamine, which probes the release of dopamine within the mesocorticolimbic system, a major component of the brain reward system, and produces measurable behavioral changes, including rewarding effects (eg, euphoria). We hypothesized that depressed individuals would exhibit an altered response to dextroamphetamine due to an underlying brain reward system dysfunction reflected by anhedonic symptoms.

Methods: In a double-blind, placebo-controlled, randomized, parallel study, the behavioral and physiological effects of a single 30-mg dose of oral dextroamphetamine sulfate were measured. Forty patients with a diagnosis of DSM-IV major depressive disorder who were not taking antidepressant medications (22 assigned to dextroamphetamine and 18 to placebo) were compared with 36 control subjects (18 assigned to dextroamphetamine and 18 to placebo) using validated self-report drug effect measurement tools (eg, the Addiction Research Center Inventory), heart rate, and blood pressure.

Results: Multiple regression analysis showed that severity of depression as measured by the Hamilton Rating Scale for Depression correlated highly with the rewarding effects of dextroamphetamine in the depressed group (model $R^2=0.63$; interaction $P=0.04$). A subsequent analysis categorizing the depressed group into patients with severe symptoms (Hamilton score $>23$) and those with moderate symptoms revealed a significant interaction between drug and depression ($P=0.02$). Patients with severe symptoms reported rewarding effects 3.4-fold greater than controls.

Conclusions: The results suggest the presence of a hypersensitive response is present in the brain reward system of depressed patients, which may reflect a hypofunctional state and may provide a novel pathophysiologic and therapeutic target for future studies.

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The pathophysiology of major depressive disorder (MDD) consists of functional changes in the neurotransmitter and neuroendocrine systems, such as the monoamines and the hypothalamic-pituitary-adrenal axis, as well as functional neuroanatomical changes in the cingulate, insula, amygdala, basal ganglia, caudate, and frontal, prefrontal, parietal, and temporal lobes, some of which are consistent with postmortem findings. Despite evidence of complex neurobiological mechanisms, the therapeutic targets of novel antidepressants remain based on the monoamine hypothesis of depression, selectively restoring the function of specific monoaminergic systems, without evidence of improved efficacy compared with older classes. Although MDD is defined as a disorder comprising disturbances in emotional and motivational processing along with various somatic and endocrine changes, it is more plausible to study the symptoms rather than the syndrome given the involvement of multiple interacting neurotransmitters and pathways. We chose to target a specific neurobiological mechanism, the brain reward system (BRS), which may underlie specific and core symptoms of MDD, such as the loss of pleasure or interest (anhedonia). The BRS consists of extensive neural pathways that mediate behavioral components of reward such as pleasure and motivation. The mesocorticolimbic dopamine system is among the most studied BRS pathway in animal models and has recently been implicated in human BRS studies of nicotine, cocaine, and dextroamphetamine reward. Reinforcing drugs (eg, psychostimulants and opiates) possess significant abuse potential because of their ability to stimulate BRS pathways, such as mesocorticolimbic dopamine by...
PARTICIPANTS AND METHODS

PARTICIPANTS

Patients with depression were of either sex; were aged 18 to 63 years; met DSM-IV criteria for MDD; and were not using antidepressant medications for at least 2 weeks (5 weeks for fluoxetine). Patients were referred by collaborating psychiatrists from 3 mood disorder clinics in Toronto or were recruited through city newspaper advertisements or telephone surveys. Patients recruited from advertisements or surveys were assessed using the Structured Clinical Interview for the DSM-IV by a trained researcher and were also assessed by a staff psychiatrist for diagnostic confirmation and physical health. Exclusion criteria specific to patients with MDD included current suicidal ideation posing an immediate threat to the person’s life and comorbid DSM-IV Axis I mental illness, including other mood disorders (eg, bipolar disorder) and substance use disorders.

Controls (n = 36) were recruited by word of mouth and were assessed by a trained researcher. They were excluded if their Hamilton Rating Scale for Depression (HAM-D) (21 items) score was greater than 6 or if they had a personal history of mood disorders or other psychiatric illnesses.

Exclusion criteria included the following: a current or past history of cardiovascular disorder, a medical condition requiring investigation or treatment, recent (<1 year) or current DSM-IV–defined psychoactive substance use (eg, alcohol) disorders, except nicotine and caffeine, pregnancy/lactation, or current use of any medication known to interact with the study drug (eg, opioid analgesics).

To recruit the MDD group, 238 individuals were contacted through referrals and advertisements: 64 were eligible and 53 were ineligible mostly because they were already taking antidepressant medications or reported another DSM-IV Axis I mental illness (eg, bipolar disorder). The remaining potential participants were not screened owing to cancellation of appointments or inability to be contacted. Of the 64 patients who were eligible, 42 completed the study session and the remainder did not attend their appointments. Of the 42 completers, 2 were excluded because of protocol violations (1 for use of bupropion hydrochloride and methotrexate and 1 for use of sedatives).

The protocol was approved by the research ethics board of Sunnybrook & Women’s College Health Sciences Centre or the Centre for Addiction and Mental Health. Signed informed consent was obtained from all participants.

PROCEDURE

This was a between-subject, randomized, double-blind, placebo-controlled, parallel study. Comparisons were made between patients diagnosed as having MDD and control subjects and between individuals receiving placebo and dextroamphetamine, resulting in 4 initial study arms: MDD-dextroamphetamine, MDD-placebo, control-dextroamphetamine, and control-placebo.

Dextroamphetamine sulfate (Dexedrine, SmithKline Beecham Pharmaceuticals, Chicago, Ill) and placebo doses were prepared in identical 10-mg capsules filled with dextrose or dextrose powder. A research pharmacist dispensed the medication and kept the randomization code.

After standardized screening based on previously described participant criteria, volunteers were seen between 8 and 10 AM for a study session. A urine sample was collected to assess compliance (ie, toxicology screen). Symptom severity was assessed using scales described in the “Assessments” subsection. After a light standardized breakfast, participants completed a baseline cycle (before drug administration) of computerized behavioral measurements (eg, the Addiction Research Center Inventory [ARCI]). Baseline physiological measurements (eg, heart rate) were also recorded. Patients then ingested 30 mg of dextroamphetamine or placebo. Behavioral and physiological measurements were repeated 30, 60, 120, 180, and 240 minutes after drug administration to capture the rise, peak, and downslope of the response. Blood samples were drawn at baseline and 120 minutes after drug administration (near the peak time of subjective effects) to evaluate levels of homovanillic acid (HVA) (a dopamine metabolite) and only at 120 minutes for plasma drug concentrations. Gas chromatography–mass spectrometry was used for HVA detection with a
deuterated HVA as the internal standard, which has been described previously using cerebrospinal fluid instead of plasma. Dextroamphetamine concentrations were determined using gas chromatography–mass spectrometry.

ASSESSMENTS

The Beck Depression Inventory, the Snith-Hamilton Pleasure Scale (SHAPS), and a modified version of the Sunnybrook Psychomotor Agitation and Retardation Questionnaire, all self-report instruments, were administered before drug ingestion only (ie, at baseline) to evaluate depression, anhedonia, and psychomotor symptom severity, respectively. Severity of depressive episodes experienced by patients during the 2 to 3 weeks before the study session day was evaluated using the HAM-D. Heart rate and blood pressure—the physiological, objective drug effect measures—were recorded by a trained researcher using a stethoscope and a sphygmomanometer. Instruments used to measure behavioral (subjective) drug effects were computerized versions of the Addiction Research Center Inventory (ARC1) the Profile of Mood States (POMS), and the Visual Analogue Scale (VAS). The ARCI, the main outcome measure of dextroamphetamine rewarding effects, is composed of questions designed to measure characteristic positive effects of drugs that are reinforcing (ie, that can promote drug self-administration) and negative effects (eg, increased anxiety and agitation). Specific sets of these questions (eg, “I feel now as I have felt after a very exciting experience; I feel so good I know people can tell it”) belong to empirically derived scales validated to measure characteristic effects of drugs or drug classes (eg, Amphetamine, Stimulation-Euphoria, and Unpleasantness Dysphoria). The POMS and the VAS are additional, less specific self-report measures administered to assess acute mood changes.

DATA ANALYSIS

The peak dextroamphetamine behavioral effect was defined as the highest scale score among the 60-, 120-, and 180-minute recordings. The corresponding baseline score was subtracted from this value to measure the change. The main dependent outcome variable, termed ARC1 Rewarding Effects Composite, consisted of a composite of change scores from scales that measure positive reinforcing effects: Abuse-Potential, Amphetamine, Benzodine, Morphine-Benzodine, and Stimulation Euphoria. Similar rewarding effects composites were calculated with the POMS using the Elation, Vigor, and Friendliness scales and with the VAS using the peak “I like the drug,” “I feel an increase in energy,” “I feel high,” and “I feel the drug’s good effects” scales. An ARC1 Negative Effects Composite measure was also calculated by grouping the change scores from the Pentobarbital Chlorpromazine Alcohol Group, LSD, Sedation-Motor, Sedation-Mental, Unpleasantness-Physical, and Unpleasantness-Dysphoria scales to evaluate increases in negative (ie, unpleasant) drug effects. Because of the different score ranges within the various scales, baseline and peak scores were converted to a score on a 100% scale before being added into the composite score. The Cronbach α coefficient was obtained for each composite measure to evaluate internal consistency.

Data were analyzed by simple factorial analysis of covariance (ANCOVA) using a statistical software program (SPSS version 10.0.0; SPSS Inc, Chicago, Ill). The effects of the independent variables, mood (depressed vs control) and drug (dextroamphetamine vs placebo), as well as the interaction were tested (α = .05, 2-tailed). Age and sex were included as covariates for all ANCOVAs. In addition to modeling mood as a dichotomous variable, we also modeled depression as a continuous variable using the actual HAM-D score. That is, multiple regression analysis was applied in the MDD group to examine the effect of drug (dextroamphetamine vs placebo), HAM-D score, and the interaction, adjusting for age and sex. Demographic and baseline measurements (ie, before drug administration) were compared using independent samples t tests. Pearson correlation coefficient tests were used for bivariate correlations.

### Characteristics of 40 Patients With Major Depressive Disorder (MDD) vs 36 Control Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MDD Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.15 ± 10.67</td>
<td>31.83 ± 11.02</td>
</tr>
<tr>
<td>Sex, M/F, No.</td>
<td>13/27</td>
<td>24/12</td>
</tr>
<tr>
<td>Hamilton Rating</td>
<td>23.35 ± 5.24</td>
<td>0.81 ± 1.33</td>
</tr>
<tr>
<td>Scale for Depression score</td>
<td>26.90 ± 8.54</td>
<td>1.97 ± 2.95</td>
</tr>
<tr>
<td>Beck Depression Inventory score</td>
<td>5.10 ± 3.72</td>
<td>0.71 ± 1.35</td>
</tr>
<tr>
<td>Scale score</td>
<td>3.25 ± 2.39</td>
<td>4.11 ± 2.33</td>
</tr>
<tr>
<td>Education, y</td>
<td></td>
<td></td>
</tr>
</tbody>
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*Data are given as mean ± SD except where indicated otherwise.

Differences within the MDD Group

Multiple linear regression analysis (described in the “Data Analysis” subsection) revealed that severity of depression, as measured by the HAM-D, correlated strongly with the degree of dextroamphetamine rewarding effects reported by patients with MDD. The R² for the model was 0.63, and the P value for the interaction between drug and HAM-D score was .04 (Figure 1). Similar but less robust trends occurred between the HAM-D and the...
POMS ($R^2=0.44$; interaction $P=0.08$) and the VAS ($R^2=0.43$; interaction $P=0.35$) reward composites.

Pearson correlation tests revealed that the ARCI Rewarding Effects Composite scores of the MDD-dextroamphetamine group correlated positively with the HAM-D item score, which most closely measures anhedonic symptoms, that is, loss of interest in work and activities (items 7) ($r=0.45; P=0.03$) and decreased libido (item 14) ($r=0.51; P=0.02$). Psychomotor Retardation scores correlated positively with HAM-D ($r=0.33; P=0.04$) and Beck ($r=0.57; P<0.001$) scores; SHAPS (anhedonia) scores correlated with Beck scores only ($r=0.38; P=0.02$).

**DEXTROAMPHETAMINE EFFECTS: PATIENTS WITH MDD VS CONTROLS**

The originally planned analysis described in the “Data Analysis” subsection, ANCOVA treating mood as a dichotomous variable (MDD vs control), did not reveal differences between the MDD and control groups on all outcome measures of dextroamphetamine behavioral effects, including the ARCI Rewarding Effects Composite score, which showed no interaction between mood and drug ($F_{1.70}=1.54; P=.22$). The lack of significance in this ANCOVA was probably due to the large variation in Rewarding Effect Composite scores in the MDD group, variation explained by the degree of depression (Figure 1). Thus, patients with MDD could not be treated as a homogeneous group. We separated patients with MDD into 2 groups—severely depressed and moderately depressed—using the median and mean HAM-D score found in this study (HAM-D score, 23), resulting in 6 study arms: severe-dextroamphetamine (n=11), severe-placebo (n=8), moderate-dextroamphetamine (n=11), moderate-placebo (n=10), control-dextroamphetamine (n=18), and control-placebo (n=18).

In the ANCOVA model testing differences in ARCI Rewarding Effects Composite scores, adjusting for age and sex, the interaction between depression severity (severe vs moderate vs control) and drug (placebo vs dextroamphetamine) was significant ($F_{2.66}=4.29; P=0.02$), where patients with severe depression showed a dextroamphetamine effect 3.4-fold greater than controls (Figure 2). The same trend occurred with the POMS ($F_{2.66}=3.10; P=0.052$) and VAS ($P=NS$) Rewarding Effects Composite scores. Statistical differences in ARCI Negative Effects Composite scores were not found between groups. The time course of the dextroamphetamine or placebo effect in the 6 groups is displayed in Figure 3.

The Cronbach $\alpha$ was 0.96 for the ARCI Rewarding Effects Composite, 0.87 for the ARCI Negative Effects Composite, 0.87 for the POMS Rewarding Effects Composite, and 0.83 for the VAS Reward Composite, confirming the reliability of the scale pooling method.

Physiological response differences were unlike those of the behavioral response. No differences were found between the MDD and control groups for dextroamphetamine-induced increases in blood pressure, which on
average increased 21/14 mm Hg. The ANCOVA including drug (dextroamphetamine vs placebo), severity (control vs moderate vs severe), and their interaction, with age and sex as covariates, showed that there was a greater increase in heart rate for the moderate group: 19 beats/min compared with 8 beats/min for the control-dextroamphetamine group and 11 beats/min for the severe-dextroamphetamine group (F2,68 = 4.70; P = .01). There was no correlation between the degree of physiological and behavioral dextroamphetamine measurement scores.

The t test results comparing demographic and baseline characteristics in patients with moderate vs severe depression showed significantly higher HAM-D, Beck, and Psychomotor Retardation scores in the severe group (P < .05 for all characteristics). Age, sex, SHAPS (anhedonia scale) scores, Psychomotor Agitation scores, education, substance use history, and baseline scores in physiological and behavioral (eg, ARCI) measures were similar.

BASELINE DIFFERENCES BETWEEN PATIENTS WITH MDD AND CONTROLS

Baseline heart rate and blood pressure differences did not occur between the MDD and control groups. However, compared with controls, the mean baseline (ie, before drug administration) score in the ARCI Rewarding Effects Composite was 1.5-fold lower (t52 = 6.84; P < .001) in the MDD group. To rule out the possibility that the increased rewarding effects seen in patients with MDD were due solely to lower baseline scores, we also tested differences in the raw peaks of the groups. Results showed that the interaction between severity and drug remained significant (F2,68 = 3.51; P = .04), with an age- and sex-corrected, placebo-controlled dextroamphetamine effect of 165.68 (95% confidence interval, 91.53-239.84) for the severe group, 49.17 (95% confidence interval, 20.54-118.88) for the moderate group, and 53.92 (95% confidence interval, 0.64-107.20) for the control group. Thus, without the effect of baseline, the dextroamphetamine peak effect was 3-fold greater in patients with severe depression compared with controls. A significant interaction also occurred using peak POMS composite scores (F2,68 = 3.56; P = .03). As with the baseline-corrected scores used in Figure 1 (ie, the ARCI Rewarding Effects Composite scores), similar results were found with the raw peak values (model R2 = 0.52; interaction P = .02). Moreover, baseline ARCI Rewarding Effects Composite scores of patients with MDD did not correlate with depression severity (ie, HAM-D score), showing that the relationship seen in Figure 1 was also unaffected by initial baseline scores.

DEXTROAMPHETAMINE AND HVA LEVELS

Adverse effects related to dextroamphetamine administration were few, mild, and reversible (eg, restlessness and anxiety). The mean plasma dextroamphetamine level was 42 ± 16 ng/mL. Drug (placebo vs dextroamphetamine) or mood (control vs moderate vs severe) did not interact with HVA concentrations (mean, 69 ± 30 ng/mL at baseline and 51 ± 28 ng/mL at the 120-minute measurement).

The main findings of our study are as follows: (1) There was a strong positive relationship between degree of MDD severity and degree of dextroamphetamine rewarding effects. (2) Patients with MDD and severe symptoms (those with HAM-D scores > 23) experienced a greater degree of rewarding effects compared with controls, whereas patients with moderate depression were not different from controls. The HAM-D score separating the MDD groups was determined mathematically (ie, median and mean), and although there is no standardized definition for severe depression, this cutoff value (HAM-D score, 23) is clinically relevant.55 Intragroup variations found in controls were within those observed in other studies.34,56,57 Patients with more severe symptoms reported a greater change relative to their baseline and a greater absolute peak dextroamphetamine effect compared with controls, findings not confounded by sex and age. Results confirm that the behavioral effects of dextroamphetamine are distinguishable from the cardiovascular effects and that HVA levels are not altered by dextroamphetamine administration.35,58-61 The results in Figure 1 and Figure 2 also show that patients with severe depression given placebo reported higher ARCI scores than the control and moderate groups, findings that will be discussed elsewhere (L.K.T., C.A.N., L.C., N.H., and U.E.B., unpublished data, 2002).

These results demonstrate the importance of the severity of MDD in the study of potential brain mechanisms. Symptom severity previously has been shown to be an important factor for the interpretation of data in neuroimaging studies with psychiatric patients.62,63 and
subjective response to a psychostimulant. The findings in this study could explain previous large discrepancies in the literature regarding the direction of dextroamphetamine response in patients with depression. De Wit et al reported that individuals with various diagnoses of depression (minor depression, dysthymia, and MDD) and a total mean HAM-D score of 12 showed no differences in their response to oral administration of dextroamphetamine (10 mg) compared with controls, which is in concordance with our findings in the moderately depressed group. Past studies using dextroamphetamine as a predictor for tricyclic antidepressant response have shown that patients who are depressed report dextroamphetamine effects, but findings were inconsistent, making dextroamphetamine a poor prognostic tool. However, these studies used observer rating scales or did not assess rewarding effects, did not compare responses with controls, were often not placebo controlled, and were characterized without proper diagnostic criteria and/or recruited a patient group with different mood disorders, such as bipolar disorder together with MDD.

These results provide support for the hypothesis that an altered response to the rewarding effects of dextroamphetamine occurs in MDD due to an underlying BRS dysfunction. The importance of dopamine for BRS function, the ability of dextroamphetamine to stimulate this system at the mesoaccumbens (primarily through presynaptic dopamine-releasing effects but also through inhibition of the dopamine reuptake system), and the evidence linking dextroamphetamine behavioral effects to dopamine binding onto D1 receptors in important BRS substrates together suggest that the proposed BRS dysfunction may involve dopaminergic mechanisms within the BRS. Furthermore, changes in dopamine activity have recently been associated with changes in regional blood flow in the cingulate and the frontal cortex, regions implicated in the pathophysiology of depression.

An enhanced response to a BRS probe such as dextroamphetamine may reflect decreased output, in which compensatory mechanisms (eg, secondary up-regulation of dopamine receptors) can be activated by an exogenous source (eg, dextroamphetamine) and can generate a supersensitive response. The dopaminergic system can exhibit important plastic changes. A dopamine storage deficit is unlikely because experimental depletion of dopamine in unmedicated patients with MDD does not produce exacerbation of symptoms. Studies using equivalent neuroimaging techniques and radioligands with comparable mean HAM-D scores have looked at dopamine D3 receptor densities in patients with MDD vs controls, yielding inconsistent results. However, the study by Ebert et al found increased binding (ie, reflecting up-regulation) in the patient group with psychomotor retardation, a symptom that was more severe in this study’s severely depressed group compared with the moderately depressed group. The degree of psychomotor retardation correlates with the degree of anhedonia, and anhedonia correlates with the degree of self-reported depression severity, findings confirmed in this study. In addition to receptor changes, decreased presynaptic dopamine function has been found in patients with MDD and affective flattening and psychomotor retardation. It may be argued that because of the ability of dextroamphetamine to release neurotransmitters other than dopamine, the differences in response between severely depressed and control subjects may be attributed to noradrenergic, serotonergic, or cholinergic mechanisms. The evidence regarding the involvement of these neurotransmitters in dextroamphetamine-induced rewarding effects in humans does not support this possibility; however, one cannot discount the possibility that they may modulate the BRS dopamine pathways in MDD.

A limitation of this study is that one measure of anhedonia, the SHAPS, was not predictive of the level of dextroamphetamine effects, as was shown in Figure 1 with the HAM-D. One challenge is that anhedonia is present in most patients and is a core symptom of MDD. Thus, the SHAPS score may more likely measure a depressed mood state rather than being a subtyping factor in data analysis. Nevertheless, the item within the HAM-D that most closely measures anhedonia (ie, loss of interest in activities), and decreased libido, a symptom that may also be modulated by the BRS, showed a positive correlation with dextroamphetamine reward. A greater number of patients, particularly men, with MDD; an improved measure of anhedonia (eg, with less cultural bias and preselected pleasures); and additional measures of reward that cover aspects other than pleasure (eg, motivation task) would strengthen the relationship between altered BRS function in MDD and anhedonic symptoms. Testing BRS function in remitted nonmedicated patients with MDD would also shed light on the state vs trait question, that is, whether a BRS dysfunction represents an underlying brain mechanism for symptoms in MDD or is a trait that affects the course of the illness.

In conclusion, the BRS may be an important therapeutic target to relieve anhedonia, a core symptom in MDD, and psychomotor retardation. Furthermore, studies are implicating the mesocorticolimbic dopamine system in functions other than reward behavior, such as stress, emotion, and cognition, which are pertinent for the study of the pathophysiology of MDD.

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REFERENCES

Correction

Error in Table Numbers. In the Commentary titled “Lowered Estimates—but of What?” (Arch Gen Psychiatry. 2002;59:129-130), the sentence referring to Tables 3 and 7 of the original article should have read as follows: “For example, Tables 2 and 6 in the article by Narrow and colleagues imply that of patients meeting NCS major depression criteria, 29% of those with suicidal ideation (about 1.2% of the US population), 19% of those with suicidal attempts, 36% of those unable to work for 2 days or more in the last month, and 31% of those who had to cut back on work in the last month fail to satisfy the CS.” The ARCHIVES regrets the error.