Brain Monoamine Oxidase A Binding in Major Depressive Disorder

Relationship to Selective Serotonin Reuptake Inhibitor Treatment, Recovery, and Recurrence

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Context: Highly significant elevations in regional brain monoamine oxidase A (MAO-A) binding were recently reported during major depressive episodes (MDEs) of major depressive disorder (MDD). The relationship between MAO-A levels and selective serotonin reuptake inhibitor (SSRI) treatment, recovery, and recurrence in MDD is unknown.

Objectives: To determine whether brain MAO-A binding changes after SSRI treatment, whether brain MAO-A binding normalizes in subjects with MDD in recovery, and whether there is a relationship between prefrontal and anterior cingulate cortex MAO-A binding in recovery and subsequent recurrence of MDE.

Design: Case-control study.

Setting: Tertiary care psychiatric hospital.

Participants: Twenty-eight healthy subjects, 16 subjects with an MDE secondary to MDD, and 18 subjects with MDD in recovery underwent carbon 11–labeled harmine positron emission tomography scans. Subjects with MDE were scanned before and after 6 weeks of SSRI treatment. All were otherwise healthy, nonsmoking, and medication free. Subjects with MDD in recovery were followed up for 6 months after MAO-A binding measurement.

Main Outcome Measure: Monoamine oxidase A VT, an index of MAO-A density, was measured in the prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, dorsal putamen, ventral striatum, thalamus, anterior temporal cortex, midbrain, and hippocampus.

Results: Monoamine oxidase A VT was significantly elevated in each brain region both during MDE and after SSRI treatment as compared with healthy controls. During recovery, MAO-A VT was significantly elevated in each brain region; however, those who went on to recurrence had significantly higher MAO-A VT in the prefrontal and anterior cingulate cortex than those who did not.

Conclusions: Elevated MAO-A binding after SSRI treatment indicates persistence of a monoamine-lowering process not present in health. This provides a strong conceptual rationale for continuing SSRI treatment during early remission. Greater MAO-A binding in the prefrontal and anterior cingulate cortex in subjects with MDD in recovery and its association with subsequent recurrence argue that deficient monoamine neuro-modulation may persist into recovery and contribute to recurrence.
sion tomography (PET) study.\textsuperscript{3} \textsuperscript{[11C]harmine is a selective, reversible PET radiotracer, with high brain uptake that binds with high affinity to MAO-A.\textsuperscript{4,7} Monoamine oxidase A is an enzyme found mainly on outer mitochondrial membranes that has an important role in the brain because it metabolizes serotonin, norepinephrine, and dopamine.\textsuperscript{8,9}} Given the 2-SD effect size in MAO-A brain because it metabolizes serotonin, norepinephrine, mitochondrial membranes that has an important role in the oxidase A is an enzyme found mainly on outer mito-

mission in more than 40% of cases\textsuperscript{15} and high rates of relapse/recurrence during SSRI treatment that reach 20% over 2 years.\textsuperscript{16} The second question addressed in this study is does greater MAO-A binding occur during MDD in recovery. While monoamine dysregulation during MDD is most frequently investigated during MDE, there are reasons to suspect that the ability to regulate monoamines is impaired even in recovery. The most compelling evidence is that most studies report greater vulnerability to mood lowering in unmedicated subjects with MDD in recovery after tryptophan depletion and after dopamine and norepinephrine depletion.\textsuperscript{17-21} Given these findings, the second main hypothesis of this study is that MAO-A binding will be elevated to a moderate extent in subjects with MDD in recovery. Within this second question is an additional issue, namely, does greater MAO-A binding associate with subsequent recurrence of MDE? Greater MAO-A binding can be viewed as a monoamine-lowering process and it has been observed that chronically lowering monoamines, such as through reserpine administration, is associated with subsequent onset of MDEs.\textsuperscript{24,25} Therefore, an addi-

Table 1. Demographic and Clinical Characteristics Data of Healthy Subjects, Depressed Subjects, and Subjects With MDD in Recovery

<table>
<thead>
<tr>
<th>Age, y, mean (SD)</th>
<th>Healthy (n=28)</th>
<th>Depressed (n=16)</th>
<th>MDD in Recovery (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRSD score, mean (SD)</td>
<td>0.61 (0.94)</td>
<td>23.81 (2.97)</td>
<td>1.17 (1.58)</td>
</tr>
<tr>
<td>Age at onset, y, mean (SD)</td>
<td>NA</td>
<td>20.38 (8.97)</td>
<td>19.28 (5.2)</td>
</tr>
<tr>
<td>No. of episodes, mean (SD)</td>
<td>0</td>
<td>2.38 (1.36)</td>
<td>3.65 (3.72)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>15 (54)</td>
<td>7 (44)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>13 (46)</td>
<td>9 (56)</td>
<td>10 (56)</td>
</tr>
<tr>
<td>Previous antidepressant treatment, No. (%)</td>
<td>NA</td>
<td>8 (50)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>Melancholic depression, No. (%)</td>
<td>NA</td>
<td>2 (12.5)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Family history of depression, No. (%)</td>
<td>0</td>
<td>2 (12.5)</td>
<td>7 (39)</td>
</tr>
</tbody>
</table>

Abbreviations: HRSD, 17-item Hamilton Rating Scale for Depression; MDD, major depressive disorder; NA, not applicable.

METHODS

PARTICIPANTS

There were 3 groups of subjects: 28 healthy subjects (mean [SD] age, 31.6 [7.6] years, 15 men and 13 women), 16 subjects with MDE with MDD (mean [SD] age, 31.9 [8.4] years, 7 men and 9 women), and 18 subjects with MDD in recovery (mean [SD] age, 31.1 [8.3] years, 8 men and 10 women). Subjects with MDE were scanned before and after 6 weeks of SSRI treatment; of the 16 subjects with MDE, 15 returned for the second \textsuperscript{[11C]harmine PET scan after treatment. All other subjects were scanned once. The sample of subjects with MDE is a different sample from that gathered for the earlier study by Meyer et al.\textsuperscript{12} Participants were within the age range of 19 to 49 years. Demographics for each group are listed in Table 1. For each study participant, written consent was obtained after the procedures had been fully explained. The study and recruitment procedures were approved by the Research Ethics Board for Human Subjects at the Centre for Addiction and Mental Health, University of Toronto.

All participants were physically healthy, did not smoke cigarettes, and had no history of neurotoxin or antipsychotic use. Participants were nonsmoking because cigarette smoking may lower MAO-A levels, which would create greater variability in MAO-A binding.\textsuperscript{5} Women in perimenopause or menopause were excluded. Healthy participants were screened to rule out...
any Axis I disorders, and participants with MDD (with MDE and in recovery) were screened to rule out any comorbid Axis I disorders using the Structured Clinical Interview for DSM-IV. All participants were screened to rule out borderline and antisocial personality disorder using the Structured Clinical Interview for DSM-IV for Axis II disorders. All subjects underwent common blood tests to rule out medical causes of disturbed mood (thyroid function, electrolyte levels, and complete blood cell count). All participants underwent a urine drug screen on the day of the [11C]harmine PET scan. Use of over-the-counter medications and herbal remedies was exclusionary. Herbal remedies could not have been taken in the previous 3 months and over-the-counter medications/other medications could not have been taken in the previous month before scanning.

Subjects with current MDE were required to be antidepressant free for at least 6 months. No subject with current MDE had received antidepressant treatment within the past 7 months and 9 of the 16 patients with MDE had never received antidepressant treatment. Subjects with MDD in recovery were required to be antidepressant free for at least 1 year and not to have experienced an MDE for at least 1 year.

For all patients with MDD, a diagnosis of MDE secondary to MDD was based on the Structured Clinical Interview for DSM-IV for Axis I disorders and consultation with a psychiatrist (J.H.M.). Additional exclusion criteria for all subjects with MDD included MDE with psychotic symptoms, bipolar disorder (type I or II), history of neuroleptic use, history of self-harm or suicidality outside episodes of depression, and history of alcohol or other drug abuse. For patients with MDE, the minimum severity for enrollment was based on a cutoff score of 20 on the 17-item Hamilton Rating Scale for Depression. Subjects with MDE were treated with either citalopram hydrobromide with a titrating dose of 20 mg/d in the first week and 40 mg/d thereafter for 6 weeks or sertraline hydrochloride with a titrating dose of 50 mg/d in the first week and 100 mg/d thereafter for 6 weeks.

For subjects with MDD in recovery, a cutoff score of 7 or less on the 17-item Hamilton Rating Scale for Depression was required. Subjects with MDD in recovery were followed up for 6 months. They were assessed every 3 months (to cover the pre- and post-treatment period) and in recovery were encouraged to recontact the investigators (J.H.M., unpublished data, 2006).

The kinetics of [11C]harmine can be described with an unconstrained 2-tissue compartment model. Highly identifiable fits with the unconstrained 2-tissue compartment model are obtainable for the V1 and may be readily determined for large data sets. The V1 is an index of harmine binding and represents the concentration of the total bound radiotracer in tissue relative to plasma concentration at equilibrium. The V1 can be expressed in terms of kinetic rate parameters as follows:

\[
V_1 = \frac{k_i}{k_e} \times \left( \frac{k_i}{k_e} + \frac{K_i}{k_e} \right),
\]

where \(k_i\) and \(k_e\) are influx and efflux rates for radiotracer passage across the blood-brain barrier and \(k_i\) and \(k_e\) describe the radioligand transfer between the free and nonspecific compartment and the specific binding compartment. \(K_i/k_e\) is similar among different individuals (for further details, see Ginovart et al). The [11C]harmine PET measure of the MAO-A V1 was previously found to be reliable. Under test-retest conditions, applying the methods in this study on the high-resolution research tomograph scanner, the mean absolute difference in MAO-A V1, expressed as a percentage of MAO-A V1, ranged from 5% to 12% (n=6 individuals) (J.H.M., A.A.W., S.H., et al, unpublished data, 2006).

**STATISTICAL ANALYSIS**

The primary analyses corresponded to the main hypotheses. A paired t test comparing MAO-A V1 before and after SSRI treat-
An independent-samples $t$ test comparing MAO-A VT between subjects with MDD in recovery and healthy individuals was applied to determine if MAO-A VT differed between subjects with MDD in recovery and healthy individuals. Comparisons were done in each brain region based on previous findings of elevated MAO-A binding during MDE. Finally, MAO-A VT in the prefrontal cortex and anterior cingulate cortex were compared using an independent-samples $t$ test between subjects with MDD in recovery who went on to have a recurrence and those subjects with MDD in recovery who did not go on to have a recurrence for the primary analysis, and then the same test was conducted for other regions for secondary analyses. It was planned not to include demographic variables in the analyses because it was expected that these would have no significant relationship with MAO-A binding.

**RESULTS**

As expected based on previous report, there were no effects of age or sex on levels of MAO-A VT. Therefore, these variables were not included in subsequent analyses.

**EFFECT OF SSRI TREATMENT ON MAO-A VT IN SUBJECTS WITH CURRENT MDE**

Within the subjects with a current MDE, the mean MAO-A VT was similar before and after SSRI treatment in each region (paired $t$ test, $t_{14}=0.42-1.88; P=.68-.08$). Post-treatment values were 1.6% to 9.2% less than pretreatment values (Figure 1). As would be expected in a sample of non–cigarette smoking, medication-naïve/medication-free, depressed subjects with no comorbid psychiatric or medical illness, a high proportion responded to treatment: 12 subjects had a remission, 3 were nonresponders, and 1 was a partial responder. Fifteen subjects completed both [11C]harmine PET scans. Post hoc analysis found no relationship between SSRI type and change in MAO-A VT in any region (repeated-measures analysis of variance, effect of medication type, $F_{1,13}=0.006-0.82; P=.94-.82$). Post hoc analysis showed no effect of lifetime antidepressant treatment exposure on baseline MAO-A VT (independent-samples $t$ test, $t_{13}=1.23-0.16; P=.24-.88$).

**COMPARISON OF MAO-A VT BETWEEN HEALTHY SUBJECTS, SUBJECTS WITH CURRENT MDE, AND SUBJECTS WITH MDD IN RECOVERY**

The subjects with MDD in recovery had significantly higher MAO-A VT than healthy subjects in each region (independent-samples $t$ test, $t_{44}=2.3-4.9; P=.03$ to $P<.001$). Consistent with our previous report in a different sample, the subjects with a current MDE also had a significantly higher MAO-A VT than healthy subjects in each region (independent-samples $t$ test, $t_{42}=2.8-5.2; P=.007-.001$) (Figure 2). As expected, given the elevation in MAO-A VT prior to treatment in the MDE group, and the lack of change in regional MAO-A VT with treatment in the MDE group, regional MAO-A VT was elevated in the SSRI-treated state as compared with healthy controls (independent-samples $t$ test, $t_{41}=1.9-3.8; P=.06-.001$). Post hoc analysis showed no effect of lifetime antidepressant treatment exposure on baseline MAO-A VT (independent-samples $t$ test, $t_{13}=1.2-1.6; P=.25-.88$).

**ASSOCIATION BETWEEN MAO-A VT AND RECURRENCE**

The subjects with MDD in recovery who went on to have a recurrence had a significantly higher MAO-A VT in the prefrontal cortex and anterior cingulate cortex than those subjects with MDD in recovery who did not go on to have a recurrence (independent-samples $t$ test, prefrontal cortex and anterior cingulate cortex).

![Figure 1. Regional monoamine oxidase A distribution volume (MAO-A VT) before and after selective serotonin reuptake inhibitor treatment. Differences ranged from 1.6% to 9.2% of the original values and were nonsignificant (paired $t$ test, $P=.68-.08$).](image-url)
The first main finding is that greater MAO-A binding during MDE persists after short-term SSRI treatment. This represents a partial mismatch between SSRI treatment and disease and provides important evidence to support a new model of serotonin dysregulation after SSRI treatment of MDE in humans. The second main finding is that greater MAO-A binding occurs during recovery from MDD and is highest in those who have a recurrence in the subsequent 6 months. The second main finding argues for a scar or trait model of MAO-A binding elevation in MDD, supports a concept of ongoing monoamine deficit in relation to recurrence, and provides a new explanation for impaired monoamine regulation in MDD in recovery.

From the perspective of monoamine theory, SSRIs raise serotonin levels vigorously\(^{45-48}\) whereas elevated MAO-A levels would be expected to metabolize serotonin, norepinephrine, and dopamine excessively.\(^9\) The mismatch between monoamine levels raised by treatment and monoamine levels lowered by disease processes might, at times, contribute to lack of response to SSRI treatment. For ex-

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**COMMENT**

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**Figure 2.** Monoamine oxidase A distribution volume (MAO-A VT) in healthy subjects, depressed subjects, and subjects with major depressive disorder (MDD) in recovery. Monoamine oxidase A VT was significantly greater in each patient sample as compared with healthy subjects (*\(P<.05\), †\(P<.01\), ‡\(P<.001\)).

**Figure 3.** Monoamine oxidase A distribution volume (MAO-A VT) in subjects with major depressive disorder (MDD) in recovery: relation to subsequent recurrence. Monoamine oxidase A VT was significantly higher in subjects with MDD in recovery with recurrence as compared with other subjects with MDD in recovery in the prefrontal cortex (\(P=.02\)) and anterior cingulate cortex (\(P=.02\)) as well as the dorsal putamen, ventral striatum, and thalamus (all \(P<.05\)). Subjects with MDD in recovery with subsequent recurrence had significantly higher regional MAO-A VT than healthy subjects in all brain regions (\(P<.002\)).
ample, motor slowing during MDE is associated with receptor binding changes consistent with striatal dopamine loss, and motor slowing during MDE was recently associated with lesser likelihood of response to fluoxetine hydrochloride. From the perspective of the cellular vulnerability theory, MAO-A metabolism creates products that are potentially neurotoxic if present in excess, such as hydrogen peroxide, a reactive oxygen species. This may also reflect a mismatch between treatment and disease, since, to the best of our knowledge, it has not been demonstrated that inhibition of serotonin transporters directly influences production of reactive oxygen species.

Another important implication of persisting elevations in MAO-A levels in the SSRI-treated state is that the SSRI-treated state of an MDE is clearly not the same state as health, even when remission occurs. Greater levels of MAO-A in the SSRI-treated state can be incorporated into a new model of serotonin dysregulation during SSRI-treated MDE in humans (Figure 4). Key elements in this model include excess MAO-A, an 80% SSRI blockade at the serotonin transporter, and a modest reduction in binding of some serotonin receptors. It is well established that SSRIs block 80% of serotonin transporter sites in humans at doses that are clinically superior to placebo. In medication-free subjects with MDE, a modest reduction in cortex serotonin 2A (5-hydroxytryptamine 2A [5-HT2A]) binding potential after SSRI treatment has been reported and subjects with MDE who have had SSRI treatment within the past month often have reductions in 5-HT2A binding.

This model has strong clinical relevance. It is standard practice to maintain SSRI treatment beyond the initial 6-week trial when remission is present. This is supported by the clinical finding that cessation of antidepressant use after short-term treatment is associated with a 40% relapse rate over the subsequent 6 months whereas continuation of antidepressant treatment over the same period is associated with an 18% relapse rate. A notable implication of this model of SSRI-treated MDE is that stopping SSRI use after short-term treatment is problematic because a key monoamine-lowering process is still present. This provides a new theoretical argument to explain why it is extremely important to continue SSRI treatment to prevent relapse following the initial 6-week trial.

Greater MAO-A levels provide a mechanistic explanation for some abnormalities of receptor binding and monoamine regulation in MDD in recovery. Greater 5-HT2A binding was recently reported in medication-free subjects with MDD in recovery who had strong histories for recurrent MDD. The finding of greater MAO-A binding in recovery in the present study is consistent with this result. Greater MAO-A levels would be expected to excessively metabolize 5-HT and there is an inverse relationship between long-term manipulations of serotonin levels and cortex 5-HT2A binding. Investigations of tryptophan depletion often report more frequent mood lowering in unmedicated subjects with MDD in recovery.
ery as compared with healthy subjects. Greater MAO-A levels may explain greater vulnerability to tryptophan depletion in MDD in recovery through excess metabolism of 5-HT by MAO-A, which would facilitate loss of extracellular 5-HT. Similarly, greater MAO-A binding in MDD in recovery could explain the particular vulnerability to mood lowering after depletion of dopamine and norepinephrine after α-methylparatyrosine administration since MAO-A participates in the removal of both monoamines. Thus, greater MAO-A levels in recovery may be considered a process contributing to impaired control of monoamines.

The relationship between greater MAO-A binding in the prefrontal and anterior cingulate cortex with subsequent recurrence argues that monoamine-lowering processes contribute to recurrence of MDE. This may appear to be inconsistent with some views of the monoamine theory of MDD that suggest that low monoamine levels must occur simultaneously with reductions in mood or presence of symptoms. However, it has been reported that long periods of monoamine depletion, such as after reserpine administration, can lead to MDE in humans. Even so, the reports that long-term administration of a monoamine-lowering medication can lead to MDE are not equivalent to the idea that monoamine-lowering processes actually occur in unmedicated patients with MDD in recovery. The present study argues a new point that monoamine-lowering processes may occur during MDD in recovery and, when more prominent, are associated with recurrence.

Since greater brain MAO-A binding occurs during recovery and during MDE, greater MAO-A binding may be considered a scar or a trait. Future work will need to differentiate between scar and trait processes and identify the underlying mechanism for elevations in MAO-A binding during recovery. Etiologies to consider include both genetic, epigenetic, and hormonal influences. Unfortunately, the current intervention of SSRI treatment is not directly intervening on MAO-A binding. In the longer-term, it may be therapeutic to target the underlying processes that raise MAO-A levels in recovery so as to better prevent future MDE.

There are limitations of measurement and interpretation in this study. By using a neuroimaging ligand technique, we were able to measure MAO-A binding in vivo but the resolution of the technique does not clarify whether the binding is increased within a cell or organelle (like mitochondria membrane) or whether more MAO-A–containing cells or organelles are present. The measure of MAO-A used, an index of MAO-A density called MAO-A VT, reflects total binding, has the advantage of being computationally efficient, and is the most stable and least variable measure of [11C]Harmane binding. However, approximately 15% of this measure reflects free and nonspecific binding so it is assumed that free and nonspecific binding do not differ tremendously between groups. An elevation in MAO-A VT may also reflect greater affinity of MAO-A, although this would not change our interpretation as greater affinity of MAO-A for monoamines would be expected to contribute to monoamine loss. A limitation of the monoamine-oriented interpretations of the MAO-A binding abnormality is that the MAO-A binding abnormality may also be related to other abnormalities in MDD. For example, changes in MAO-A binding could be elevated secondary to other processes, such as mitochondrial dysfunction, that then participate in the pathophysiology of MDD.

There are also some limitations in the statistical design. The first issue is analyzing multiple data sets. There are 3 main data sets in this study: the MAO-A binding before and after SSRI treatment, the MAO-A binding in health and in subjects with MDD in recovery, and the MAO-A binding data in the subjects with MDD in recovery combined with the follow-up data for recurrence. As more data sets are analyzed in a laboratory, the likelihood of a chance finding rises. For example, after completion of 5 separate studies, each with a main significance threshold of P = .05, for which the true result should be nonsignificant in each, there would be a 25% likelihood of at least 1 significant finding due to chance alone. The second issue is that we examined multiple regions. For the main analyses of investigating how MAO-A binding changes after SSRI treatment, and the comparison of MAO-A binding between subjects with MDD in recovery and healthy subjects, all regions were included in the hypothesis. For the relationship between MAO-A binding and recurrence, the prefrontal cortex and anterior cingulate cortex regions were included in the hypothesis. For all of these findings, the expected results occurred in each of the hypothesized regions. Should it have been that only 1 region significantly met the hypothesis, then the finding could have been due to chance alone as a result of multiple comparisons. For example, in a study of 10 hypothesized regions, in which 1 region alone is significant at a P value of .05, there would be a 50% likelihood that the single regional finding was due to chance alone.

To our knowledge, this is the first study to measure brain MAO-A binding before and after SSRI treatment and brain MAO-A binding in unmedicated subjects with MDD in recovery.Monoamine oxidase A binding in all regions remained consistently elevated before and after SSRI treatment, even in subjects in remission, indicating a persistent abnormality that is inadequately targeted by SSRI treatment. It also demonstrates that the SSRI-treated state, even when symptoms are in remission, is clearly different from health and provides theoretical support for why discontinuation of SSRI use after short-term treatment is associated with a high risk of relapse. In subjects with MDD in recovery, regional MAO-A binding was also elevated, and greater levels of MAO-A binding in the prefrontal and anterior cingulate cortex were associated with recurrence. This argues that monoamine-lowering processes may occur during MDD in recovery and are associated with recurrence. Elevated MAO-A binding in recovery also provides an explanation for the frequently observed mood lowering after monoamine depletions in this group and identifies an important treatment target not previously implicated as a pathophysiological abnormality in the recovery phase of MDD.

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