ARCHIVAL REPORT

Greater Monoamine Oxidase A Binding in Alcohol Dependence

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Background: Alcohol dependence (AD) is a multiorgan disease in which excessive oxidative stress and apoptosis are implicated. Monoamine oxidase A (MAO-A) is an important enzyme on the outer mitochondrial membrane that participates in the cellular response to oxidative stress and mitochondrial toxicity. It is unknown whether MAO-A levels are abnormal in AD. We hypothesized that MAO-A V_T, an index of MAO-A level, is elevated in the prefrontal cortex (PFC) during AD, because markers of greater oxidative stress and apoptosis are reported in the brain in AD and a microarray analysis reported greater MAO-A messenger RNA in the PFC of rodents exposed to alcohol vapor.

Methods: Sixteen participants with alcohol dependence and 16 healthy control subjects underwent [^{11}C]-harmine positron emission tomography. All were nonsmoking, medication- and drug-free, and had no other past or present psychiatric or medical illnesses.

Results: MAO-A V_T was significantly greater in the PFC (37%, independent samples *t* test, $t_{30} = 3.93$, $p < .001$), and all brain regions analyzed (mean 32%, multivariate analysis of variance, $F_{7,24} = 3.67$, $p = .008$). Greater duration of heavy drinking correlated positively with greater MAO-A V_T in the PFC ($r = .67$, $p = .005$) and all brain regions analyzed ($r = .73$ to $.57$, $p = .001$–$.02$).

Conclusions: This finding represents a new pathological marker present in AD that is therapeutically targetable through direct inhibition or by novel treatments toward oxidative/pro-apoptotic processes implicated by MAO-A overexpression.

Key Words: Addictions, alcohol dependence, monoamine oxidase A, neurotoxicity, oxidative stress, positron emission tomography

Alcohol dependence (AD) is a chronic, relapsing illness with enormous societal impact, accounting for 4% of global death and 5% of the global burden of disease (1). The toxicity of chronic, excessive alcohol exposure is associated with diverse organ damage across the liver, heart, pancreas, and brain, implicating several processes including acetaldehyde formation, disturbed calcium and iron regulation, epigenetic modifications, and oxidative stress (2,3). However, despite advances in understanding the consequences of excessive alcohol intake, a paucity of neural targets have been identified with translatable potential for pharmacotherapy.

Monoamine oxidase A (MAO-A) is an important enzyme located on the outer mitochondrial membrane of glia and monoamine releasing neurons, particularly norepinephrine releasing neurons, that participates in the cellular response to mitochondrial toxicity and oxidative stress (4). MAO-A metabolizes monoamines such as serotonin, norepinephrine, and dopamine, and levels of MAO-A in brain tissue show a strong, positive correlation with MAO-A activity (5,6). Previous investigations of MAO-A activity in postmortem brain of AD were primarily negative, with no change reported in prefrontal cortex, and a decrease reported in the hypothalamus and caudate (7,8). Unfortunately, these studies were inconclusive because none of them addressed several recently discovered biases that influence MAO-A levels, such as cigarette smoking (9,10), exposure to current or past major depressive episodes (11–13), and impulsive-aggressive personality traits (14,15). The latter covary with MAO-A levels, likely because of a neurodevelopmental influence of inherited MAO-A levels (16).

Two findings suggest that elevated MAO-A level may occur in AD, particularly in the prefrontal cortex, and hence should be investigated in humans. First, markers of greater oxidative stress (2,17,18) and predisposition to apoptosis (19–21) may be present in brain and other organs in AD, and oxidative stress and mitochondrial toxicity lead to elevated MAO-A levels in neuroblastoma and glioblastoma cell lines (4,22–24). Second, a microarray analysis evaluating the effects of chronic alcohol vapor exposure in rodents reported a 2.5-fold elevation in MAO-A messenger (m)RNA in the prefrontal cortex (25). To investigate MAO-A levels in AD in humans and avoid confounding biases that influence MAO-A levels such as cigarette smoking and major depressive disorder, we chose an in vivo approach by applying [^{11}C]-harmine positron emission tomography (PET). [^{11}C]-harmine PET measures brain MAO-A V_T, an index of MAO-A density, and [^{11}C]-harmine has properties of an excellent PET radiotracer for MAO-A, including high brain uptake, selective and reversible binding, and metabolites that are not brain penetrant (10). On the basis of the association between alcohol dependence and oxidative stress and the involvement of MAO-A in cellular responses to oxidative stress, we hypothesized that MAO-A level would be elevated in the prefrontal cortex during AD. Our second main hypothesis was that greater years of exposure to heavy alcohol use would be associated with the elevation in MAO-A level.

Methods and Materials

Study Participants

Sixteen individuals with alcohol dependence (mean age, 35; SD, 8) were compared to 16 healthy controls (mean age, 34; SD, 9). Demographics are listed in Table 1. Some of the healthy

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Table 1. Demographic and Clinical Characteristics of Study Participants[a]

	Healthy Subjects (n = 16)	Alcohol Dependent Subjects (n = 16)
Age, years	34 (8.8)	35 (7.6)
Sex, Male/Female	14/2	14/2
SCID Diagnosis of Major Depressive Disorder	0	0
HAM-D	.8 (1.2)	3.7 (2.0)
VAS Depressed Mood[b]	2.5 (1.5)	4.2 (2.0)
Angry-Hostility[c]	12.1 (5.1)	12.1 (5.4)
Deliberation[c]	16.4 (3.7)	16.3 (6.0)
Alcohol Intake Behaviors		
No. drinks/day	.14 (.25)	8.0 (3.5)
No. drinking days/week	0 (0)	6.3 (.9)
Duration of alcohol dependence, years	N/A	6.3 (4.1)
Alcohol Dependence Scale	N/A	12.7 (6.9)
CIWA-Ar at scan	N/A	9.8 (1.4)

None of the healthy control subjects drank alcohol on a regular basis or had a diagnosis of alcohol dependence or withdrawal. Independent samples t tests showed no significant difference for age (t_{30} = .56, p = .58), angry-hostility (t_{30} = .002, p = .998), deliberation (t_{30} = .049, p = .962). There was a significant difference for HAM-D and VAS scores (t_{30} = 4.95, p < .001, t_{30} = 2.79, p = .009, respectively), yet all participants were below the HAM-D threshold for a major depressive episode.

CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; HAM-D, Hamilton Rating Scale for Depression; N/A, not applicable; SCID, Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders; VAS, Visual Analog Scale.

[a]Values are expressed as mean (SD).

[b]Endorsement of depressed mood on the VAS at the time of the scan.

[c]Personality facet within the Neuroticism Extroversion Openess Personality Inventory—Revised questionnaire.

participants (n = 14) participated in earlier studies (10,12). Participants were within the age range of 18 to 50 years and in good physical health.

The key inclusion criteria for the AD group was an AD diagnosis using the Structured Clinical Interview for DSM-IV (26). Severity of AD was assessed using the Alcohol Dependence Scale (27). Our intent was to recruit subjects with AD who had not acquired additional psychiatric or medical illnesses, and we chose a minimum drinking cutoff commonly associated with AD that required consuming at least 4 (for women) or 5 (for men) drinks per day at least 5 days of the week (28,29). This cutoff is a well-accepted level for hazardous drinking because consumption beyond this level across several years has an extremely high probability of leading to AD (30). In a previous study, moderate to heavy cigarette smoking was associated with greater MAO-A V_T in early withdrawal and reduced MAO-A V_T during active smoking (10); hence, cigarette smoking was an exclusion criterion in the current study. Although 50% of people with AD smoke cigarettes (31), this cutoff of alcohol consumption ensures a representative sampling of alcohol intake behavior in AD subjects, regardless of smoking status (30). Plasma aspartate aminotransferase, alanine aminotransferase, and urine ethyl glucuronide were also measured.

To avoid factors that could bias MAO-A levels in each group, exclusion criteria included any current or past Axis I or Axis II disorder (26) (apart from AD in the AD group), cigarette smoking, herbal, drug or medication use within 8 weeks of scanning, history of psychiatric or medical illness, or any other substance abuse or dependence. Lifetime history of comorbid Axis I disorders, including past major depressive episodes and anxiety disorders, were exclusionary. Screening included exhaled carbon monoxide level (MicroSmokerlyzer; Bedfont Scientific Ltd., Kent, United Kingdom), plasma cotinine levels, and a urine drug test at screening and on the day of PET scan. Those with positive results for other substances were excluded. For women, phase of menstrual cycle was recorded by self-report. In a previously collected sample, there was no relationship between phase of menstrual cycle and MAO-A V_T (32). To avoid confound from variations in plasma estrogen levels, women in early postpartum, perimenopause, or menopause were excluded. Participants were required not to drink tea or coffee on the day of scanning. All subjects reported no previous head injury and had no neurological disorders associated with alcohol dependence (Korsakoff syndrome, Wernicke's encephalography). For each participant, written consent was obtained after the procedures were 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.

Protocol on Day of PET Imaging

All study participants underwent a single [^{11}C]-harmine PET scan. Alcohol metabolism may lead to the formation of a beta-carboline compound called harman (33,34), and alcoholic beverages frequently contain harman (35), which has moderate affinity for MAO-A. To avoid temporary occupancy effects of harman (10), [^{11}C]-harmine PET scanning was timed at a point when harman levels were negligible (36), which was verified by plasma sampling. Subjects were instructed to maintain their usual alcohol intake behavior and to stop drinking at 12 A.M. the evening before the [^{11}C]-harmine PET scan. A breathalyzer screen was taken and results were consistent with recent cessation of alcohol intake. Also, before scanning, 12-cm visual analog scales for mood (i.e., happy–depressed), energy (i.e., most–least), and anxiety (i.e., relaxed–tense), and the Clinical Institute Withdrawal Assessment for measurement of severity of withdrawal symptoms, were completed. For the visual analog scales, participants were instructed to draw a vertical line crossing the 12-cm linear scale at the point corresponding to the strength of their experience of the given dimension of the mood state.

PET Image Acquisition

The PET images were obtained using a High Resolution Research Tomograph PET camera (in-plane resolution; full width at half maximum, 3.1 mm; 207 axial sections of 1.2 mm; Siemens Molecular Imaging, Knoxville, Tennessee) in a manner described previously (12). A dose of 370 MBq of intravenous [^{11}C]-harmine was administered as a bolus. The [^{11}C]-harmine was of high radiochemical purity (99.16% ± 1.12%) and high specific activity (94.27 ± 33.71 GBq/μmol) at the time of injection. The emission scan was reconstructed in 15 frames of 1 minute, followed by 15 frames of 5 minutes. An automatic blood sampling system was used to measure arterial blood radioactivity continuously for the first 10 minutes after injection. Manual samples were obtained at 2.5, 7.5, 15.0, 20.0, 30.0, 45.0, 60.0, and 90.0 minutes. The radioactivity in whole blood and plasma were measured as described previously (37).

Image Analysis

Each participant also underwent magnetic resonance imaging (GE Signa 1.5-T scanner; fast spoiled gradient echo, T_1-weighted image; x, y, z voxel dimensions, .78, .78, and 1.5 mm; GE Medical Systems, Milwaukee, Wisconsin). Regions of interest (ROIs) were

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