Decreased Striatal Monoaminergic Terminals in Severe Chronic Alcoholism Demonstrated with (+)[\(^{11}\)C]Dihydrotetrabenazine and Positron Emission Tomography

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We used (+)[\(^{11}\)C]dihydrotetrabenazine, a new ligand for the type 2 vesicular monoamine transporter, with positron emission tomography to study striatal monoaminergic presynaptic terminals in 7 male severe chronic alcoholic subjects without Wernicke-Korsakoff disease compared with 7 male normal controls of similar ages. We found reduced specific binding in the caudate nucleus and putamen in the alcoholic group, and the difference reached significance in the putamen. Specific binding was not decreased in the thalamus, which was examined as a reference structure. We also detected deficits in blood-to-brain transfer rate, \(K_t\), in the same regions of the alcoholic group, with a significant difference in the putamen. \(K_t\) was unchanged in the thalamus. The finding of reduced striatal VMAT2 in severe chronic alcoholic patients suggests that nigrostriatal monoaminergic terminals are reduced, with or without loss of neurons from the substantia nigra. The findings suggest that the damaging effects of severe chronic alcoholism on the central nervous system are more extensive than previously considered.

Severe chronic alcoholism causes major morphological changes in the human cerebral cortex and cerebellum, even in patients without Wernicke-Korsakoff disease. The changes include generalized cerebral atrophy, particularly in the frontal lobes, neuronal loss in the superior frontal region, neuronal shrinkage in the superior frontal, cingulate, and motor areas, reduced dendritic arbors of many neurons in these regions, and depletion of neurons in the anterior and superior portions of the cerebellar vermis, both in symptomatic and asymptomatic alcoholic cerebellar degeneration. These findings are consistent with changes in both anatomical and physiological imaging studies and in behavioral assessments. Anatomical imaging demonstrates focal cerebral atrophy, particularly in the frontal lobes; and physiological imaging reveals decreased local cerebral metabolic rates for glucose (CMRglc) in the medial frontal cortex, decreased CMRglc in both the cerebellar vermis and the medial frontal cortex in alcoholic cerebellar degeneration, decreased benzodiazepine receptor binding in the medial frontal cortex, and decreased benzodiazepine receptor binding in both the cerebellar vermis and the medial frontal cortex in alcoholic cerebellar degeneration. Neuro-psychological studies show abnormalities of executive function that correlate with decreased CMRglc in the frontal cortex.

Many animal studies have confirmed the focal changes observed in humans. In sufficient doses, chronic ethanol intake in rats leads to neuronal degeneration in the hippocampus, cerebellum, and prefrontal cortex. The findings in both humans and animals support the notion of selective vulnerability to alcohol-related injury in the central nervous system.

Recent evidence suggests that severe chronic alcohol-
Alcohol consumption decreases dopamine transporter densities to the striatum, nucleus accumbens, and motivation and reward, and these pathways may mediate the actions of alcohol and reinforce consumption. Several neurotransmitter systems have been implicated, including serotonin, norepinephrine, γ-aminobutyric acid (GABA), and dopamine, although the results are inconsistent. Evidence for damage to serotonergic neurons has been added from both animal investigations and human studies; however, a recent postmortem investigation demonstrated no loss of serotonergic neurons in the dorsal raphe nucleus of human chronic alcoholics. In a similar manner, injury of noradrenergic neurons has been reported in experimental animals and in some human studies, but not in others.

Recently, interest has focused on the dopaminergic neurons of the ventral tegmental area and substantia nigra in models of alcoholism. These neurons and their projections to the striatum, nucleus accumbens, and frontal cortex strongly influence behavior relevant to motivation and reward, and these pathways may mediate the actions of alcohol and reinforce consumption. Several studies have been reported in animals. In ethanol-naive alcohol-prefering rats, dopamine concentrations are reduced in the nucleus accumbens and olfactory tubercle, and catecholaminergic innervation of the dopaminergic medial mesolimbic system is decreased compared with non-alcohol preferring rats. Alcohol-prefering rats have an association between low dopamine and serotonin content in the nucleus accumbens and high alcohol preference, and the high alcohol preference can be reversed by increasing synaptic dopamine. Primate studies reveal that abstinent alcohol-prefering monkeys have increased dopamine transporter densities in comparison with alcohol-avoiding monkeys. Moreover, chronic alcohol consumption decreases dopamine transporter densities, and alcohol withdrawal reverses this effect. In a human investigation, however, dopamine transporter availability examined with [3H]-threo-methyldopa and positron emission tomography (PET) was not significantly different in alcoholic subjects compared with non-alcoholic controls, although striatal D2 receptor availability was decreased in the same patients. In studies of monoaminergic receptors, ethanol-naive alcohol-prefering rats have reduced monoaminergic and dopamine D2 receptor sites in comparison with non-alcohol preferring rats. In keeping with these findings, two investigations of dopamine D2 receptor sites, using PET and [11C]raclopride in human chronic alcoholics, revealed significantly decreased striatal D2 receptor (Bmax/KD) availability compared with nonalcoholic controls.

The present study was initiated to examine striatal monoaminergic presynaptic terminals in severe chronic alcoholics compared with normal controls, using (+)[11C]dihydrotetabenazine [(+)][11C]DBTZ] with PET to examine the density of binding to the type 2 vesicular monoamine transporter (VMAT2). Animal studies demonstrate that changing the synthesis, turnover, or release of dopamine does not result in regulation of this binding site. Hence, this ligand permits quantitative assessment of the density of striatal monoaminergic presynaptic terminals without regulatory changes from medications or disease. The previous studies in humans used ligands that bind to sites that can be regulated, and this can complicate interpretation of the results. We studied a small sample of alcoholic subjects, and compared their clinical and demographic characteristics with those of a larger group of patients we reported previously, to ensure that the current group is representative of the larger group. We have presented a preliminary report of this study.

Subjects and Methods

Patient Groups and Normal Subjects
This investigation was approved by the Institutional Review Boards of the University of Michigan Hospitals and the Ann Arbor Veterans Affairs Medical Center. We obtained informed consent from all participants. We studied 7 male severe chronic alcoholic patients (age, 52 ± 9 years) and 7 male normal controls (age, 57 ± 13 years). Six of the 7 alcoholic subjects were cigarette smokers and had smoked about one package of cigarettes daily for at least 20 years. One of the alcoholic subjects had never smoked cigarettes consistently. One of the control subjects was a cigarette smoker and had smoked about one package of cigarettes daily for at least 20 years. Six of the control subjects had never smoked cigarettes consistently. None of the alcoholic subjects had abnormalities on neurological examination except for mild cerebellar ataxia of gait in 1 subject and a mild peripheral neuropathy in another. All alcoholic subjects met diagnostic criteria for severe alcohol dependence of the Diagnostic and Statistical Manual of Mental Disorders, third edition-revised; all had been hospitalized at least once for alcoholism; and most had been sober for no more than a few months from the beginning of the chronic use of alcohol until the interval preceding participation in the present study. The duration of sobriety had a range of 3 to 9 months. These subjects were classified as heavy drinkers by existing epidemiological data, including duration and intensity of alcohol intake. We excluded alcoholic subjects with a history of polydrug abuse as defined by criteria from the National Institute on Drug Abuse; patients with neurological disorders apart from those due to alcohol, including stroke, birth complications, learning disorders, or other acquired or developmental disorders carrying neurological or neuropsychological risk, and patients with closed head injury with loss of consciousness exceeding 30 minutes.

Normal control subjects were excluded if they had a history of alcohol abuse or dependence or if they met any of the exclusion criteria of the alcoholic group. The normal controls had no history of neurological disorders and no abnormalities on general physical and neurological examinations. None of the patients or control subjects were receiving centrally active medications that influence striatal VMAT2 binding.
All alcoholic and control subjects received a complete medical and neurological history and neurological examination before entering the investigation. The subjects were studied in the absence of medications that could influence cognition, the motor system, or the PET studies, including benzodiazepines. All of the alcoholic subjects had received chlordiazepoxide 50 mg four times daily for a maximum of four days during alcohol detoxification in hospital. This medication was discontinued at least 6 weeks before PET study in all cases. The alcoholic subjects were not scanned until they had achieved at least 2 months of sobriety. When studied, all alcoholic subjects were consuming a normally nutritious diet.

Positron Emission Tomography Studies
We conducted the PET studies, using a standard protocol in all subjects. The subjects were placed on a table and asked to lie quietly, eyes open, ears unoccluded, alert but not speaking. We inserted a catheter into a radial artery for blood sampling and placed radioactive fiducial markers on the scalp to register the dynamic sequence of frames, correcting for any motion that occurred during study. We imaged the subjects with a Siemens ECAT Exact-47 PET scanner (CTI PET Systems, Inc, Knoxville, TN), which has an intrinsic in-plane resolution of 6.0 mm full-width at half-maximum (FWHM) at the center of the field of view and an axial resolution of 5.0 mm FWHM. The reconstructed resolution was approximately 9.0 mm FWHM. Forty-seven planes with a 3.375 mm center-to-center separation were imaged simultaneously. Attenuation correction was calculated by the standard ellipse method.

We prepared α-(+)-[11C]DTBZ by [11C]-methylation of α-(+)-9-O-desmethylDTBZ, with a solid phase--supported system that allows purification and isolation of the product [11C]DTBZ without high-performance liquid chromatographic purification. We administered 18 ± 1 mCi α-(+)-[11C]DTBZ containing less than 50 µg of mass of DTBZ intravenously. We collected arterial blood samples every 10 seconds for 2 minutes, then at 2.5, 3, 4, 5, 7.5, 10, 15, 20, 30, 45, and 60 minutes after injection. Samples at 1, 2, and 3 minutes and all subsequent samples were analyzed for radiolabeled metabolites, using C-18 Sep-Pak chromatography as described previously.58 We recorded a sequence of 15 scans over 60 minutes from the time of injection.

Pharmacokinetic Analysis
We performed pixel-by-pixel fitting to a two-compartment tracer kinetic model, using a weighted integration method. The analysis provided parametric images of ligand transfer from plasma to brain (Kl), which are highly correlated with flow because the single-pass extraction fraction is greater than 50%, and parametric images of total tissue distribution volume (DV) of DTBZ relative to plasma.59

Volumes of Interest Analysis
We identified anatomically configured volumes of interest (VOIs) for the caudate nucleus and putamen from parametric images of DV, then placed these structures on Kl images. We used the thalamus as a reference structure, because it is a subcortical nucleus with no known dopaminergic presynaptic terminals. We identified VOIs for the thalamus on parametric images of Kl, then placed the structure on DV images. VOIs were acquired from the two adjacent axial levels that best represented each of the three structures (caudate nucleus, putamen, and thalamus). VOIs were also acquired from the cerebral cortex of the entire brain in eight to 10 adjacent horizontal slices extending from the lowest slice containing the thalamus up to the first slice in which cortex was visualized along the entire medial surface (ie, above the level of the corpus callosum and ventricles). Values obtained from the cerebral cortical VOIs were used for normalization of data from the caudate nucleus, putamen, and thalamus. The cerebral cortex contains essentially no specific binding sites, making it an appropriate region for normalization.

Data Analysis
We used SAS60 to fit models in examining the association between diagnosis group and DTBZ Kl and DTBZ DV measurements for each of three anatomical sites (caudate nucleus, putamen, and thalamus) to determine whether differences exist between groups for these sites. The analysis was adjusted for age, using an analysis of covariance (ANCOVA) model. The primary independent variable in the analysis was the categorical variable diagnosis group (alcoholic or normal control). To determine whether cigarette smoking might have affected the data, we performed a two-way analysis of variance (ANOVA) (smoking status by alcohol group) on DTBZ DV in the putamen. No corrections were made for the effects of tissue atrophy.

Neuropsychological Tests
We examined the alcoholic subjects with a standardized test battery to compare the performance of this small group with our larger sample of alcoholic patients from previous investigations.15,17–19 Our test battery is described in previous communications.1,17–19,61 The tests incorporated into this battery were selected because of their widely known characteristics, normative standardization, and utility in producing summary indices of impairment. We selected a priori the following six summary measures of neuropsychological impairment to compare performance in the patients evaluated earlier with the 7 patients studied with DTBZ: (1) Weschsler Adult Intelligence Scale, revised (WAIS-R) Full Scale Intelligence Quotient, (2) Halstead Category Test Errors, (3) Tactual Performance Test Total Time, (4) Seashore Rhythm Test Correct, (5) Speech-Sounds Perception Test Errors, and (6) Grooved Pegboard Dominant Hand Insertion Time. We compared data from these groups by using one-tailed t tests.

Results
PET Studies
Mean DTBZ ligand influx (Kl) was decreased by 8.6% in the caudate nucleus and 6.2% in the putamen of the alcoholic group, compared with the normal control group, and was essentially unchanged in the thalamus (Table 1). Although Kl was more decreased in the caudate nucleus than the putamen, the difference reached significance at p < 0.05 only in the putamen because of the smaller variance in this structure than in the
caudate nucleus (Fig). Mean ligand \( DV \) was decreased by 4.5% in the caudate nucleus and 10.4% in the putamen of the alcoholic group, compared with the normal control group, and was essentially unchanged in the thalamus (see Table 1). The decrease of \( DV \) was significant at \( p < 0.05 \) only in the putamen.

One patient had a mild cerebellar ataxia affecting gait resulting from alcoholic cerebellar degeneration. This patient's \( DV \) was the lowest of the 7 cases for both the caudate nucleus and putamen. One patient had a mild peripheral neuropathy attributed to alcoholism. This patient's \( DV \) was the third lowest of the cases for the caudate nucleus and the second lowest for the putamen.

**Effects of Smoking**

Statistical power was limited as we had only 1 smoker in the control group and 1 nonsmoker in the alcohol dependent group. The mean levels in the putamen were 4.2 (control smoker), 3.9 (control nonsmokers), 3.7 (alcohol-dependent smokers), and 3.2 (alcohol-dependent nonsmoker), indicating an increase among smokers in both controls and alcoholics. The ANOVA \( p \) value for the smoking comparison was 0.078. The

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**Table 1. Normalized Ligand Influx \( (K_v) \) and Distribution Volume \( (DV) \) Adjusted for Age**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Controls (n = 7)</th>
<th>Alcoholics (n = 7)</th>
<th>Controls (n = 7)</th>
<th>Alcoholics (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( K_v ) (Mean ± SD)</td>
<td>( DV ) (Mean ± SD)</td>
<td>( K_v ) (Mean ± SD)</td>
<td>( DV ) (Mean ± SD)</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>1.16 ± 0.08</td>
<td>3.78 ± 0.30</td>
<td>1.06 ± 0.08</td>
<td>3.61 ± 0.30</td>
</tr>
<tr>
<td>Putamen</td>
<td>1.29 ± 0.06</td>
<td>3.93 ± 0.32</td>
<td>1.21 ± 0.06*</td>
<td>3.52 ± 0.32*</td>
</tr>
<tr>
<td>Thalamus</td>
<td>1.46 ± 0.11</td>
<td>1.34 ± 0.08</td>
<td>1.45 ± 0.11</td>
<td>1.33 ± 0.08</td>
</tr>
</tbody>
</table>

*\( p < 0.05 \), controls vs alcoholics.
as the current studies were restricted to a small cohort of alcoholic subjects, we compared demographic data and neuropsychological performance of these subjects with a larger total sample (n = 43) studied previously to determine whether the present sample is representative of the larger group. We found no significant differences between groups in age, education, lifetime alcohol consumption, or years of heavy drinking (Table 2). We also compared the neuropsychological test performance in the alcoholic subjects studied previously in our program, and the current small group of alcoholic subjects (Table 3). The results demonstrate that both groups have an average level of intelligence and show no significant differences in the degree of impairment on the neuropsychological measurements.

Discussion
This investigation using DTBZ and PET revealed decreased specific binding to VMAT2 in the caudate nucleus and putamen of severe chronic alcoholics, compared with normal control subjects, with the difference reaching significance in the putamen. Essentially no changes were seen in the thalamus, which was studied as a reference structure. Previous studies demonstrated that the VMAT2 site is not regulated, and thus diminished DTBZ binding indicates decreased density of monoaminergic presynaptic terminals. More than 95% of monoaminergic presynaptic terminals in the putamen and possibly the caudate nucleus are dopaminergic, hence, the density of dopaminergic terminals in these structures is diminished in the alcoholic group.

This reduction of striatal dopaminergic terminals may result from loss of neurons in the substantia nigra, but the present study did not address this issue. Although the results appear to be related to alcohol consumption, other factors such as thiamin deficiency and cigarette smoking, for example, could also be contributory in pathogenesis.

Comparison of the findings in the present study with others is complex, as the ligands previously used to examine striatal monoaminergic presynaptic terminals are subject to regulation. Moreover, only two studies have been published. In one, single-photon emission computed tomography with $^{[123]}$I-β-CIT showed a significant decrease in the striatal dopamine reuptake site in nonviolent alcoholics and a nonsignificant increase in violent alcoholics. In the other, PET with D-threo-$^{[11]}$C)methylphenidate reported no change in the striatal dopamine transporter even though the same subjects had decreased striatal $D_2$ receptor binding. Both $^{[123]}$I-β-CIT and D-threo-$^{[11]}$C)methylphenidate label sites that can be regulated, whereas the VMAT2 site appears not to be regulated. Thus, our finding of decreased DTBZ binding to this site may provide a more direct estimate of the density of presynaptic terminals.

In the present study, ligand influx ($K_i$) was decreased in the caudate nucleus and putamen of the alcoholic subjects, compared with the normal controls, and the difference reached significance in the putamen. $K_i$ was not decreased in the thalamus. Ligand influx provides an indication of cerebral blood flow, which is closely coupled to metabolism in the central nervous system under most conditions. The finding of decreased ligand influx in the striatum of the alcoholic

Table 2. Comparison of Alcoholic Subjects in Previous Studies and Current Investigation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Alcoholic Subjects Studied Previously (n = 43)</th>
<th>Alcoholic Subjects in Current Study (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49 ± 9</td>
<td>52 ± 9</td>
</tr>
<tr>
<td>Education (yr)</td>
<td>13 ± 2</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>Lifetime alcohol consumptionb</td>
<td>106 ± 60</td>
<td>143 ± 108</td>
</tr>
<tr>
<td>Years of heavy drinkingc</td>
<td>20 ± 10</td>
<td>21 ± 10</td>
</tr>
</tbody>
</table>

References 15, 17–19.

bEstimated number of lifetime drink equivalents (2-oz 80-proof alcohol units) in thousands.

cNumber of years of severe use of and dependence upon alcohol. Statistical testing with one-tailed t tests revealed that none of the comparisons is significant.

Table 3. Neuropsychological Performance in Alcoholic Subjects Studied Previously in this Project and Alcoholic Subjects in the Current Study

<table>
<thead>
<tr>
<th>Measure</th>
<th>Alcoholic Subjects Studied Previously (n = 43)</th>
<th>Alcoholic Subjects in Current Study (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS-R FSIQ</td>
<td>98 ± 11</td>
<td>104 ± 9</td>
</tr>
<tr>
<td>HCT (errors)</td>
<td>62 ± 31</td>
<td>78 ± 26</td>
</tr>
<tr>
<td>TPT total time (min)</td>
<td>16 ± 06</td>
<td>23 ± 11</td>
</tr>
<tr>
<td>Seashore rhythm (errors)</td>
<td>26 ± 03</td>
<td>26 ± 7</td>
</tr>
<tr>
<td>Speech sounds (errors)</td>
<td>10 ± 06</td>
<td>12 ± 7</td>
</tr>
<tr>
<td>Grooved pegboard (sec)</td>
<td>78 ± 20</td>
<td>80 ± 13</td>
</tr>
</tbody>
</table>

For all measures except WAIS-R FSIQ, higher scores indicate poorer performance. Statistical testing with one-tailed t tests revealed that none of the comparisons is significant.

References 15, 17–19.

WAIS-R FSIQ = Wechsler Adult Intelligence Scale-Revised Full Scale Intelligence Quotient; HCT = Halstead Category Test; TPT = Tactual Performance Test.
subjects suggests a diminished metabolic load in this site, probably due to reduced numbers of actively metabolizing presynaptic dopaminergic axon terminals. In keeping with this, a PET study showed persistently reduced striatal glucose metabolism in alcoholics at various intervals after withdrawal from alcohol.57

As cigarette smoking is common in alcoholism, we performed a preliminary analysis to detect differences between the smoking and nonsmoking subjects in this study. Although statistical power was limited by study of 6 smokers and only a single nonsmoker in the alcohol-dependent group and 6 nonsmokers and a single smoker in the control group, the results were surprisingly robust even though they were not statistically significant. We interpret the results as indicating that smoking may increase 

We studied a small cohort of alcoholic subjects in this study, and sought to determine whether the group is representative of the 43 patients we have investigated previously.15,17-19 To this end, we compared the ages, educational levels, and history of alcohol consumption and found no differences between groups. We also compared neuropsychological performance and here again observed no differences between the well-characterized alcoholic subjects studied previously and our current small sample investigated with DTBZ. The results provide assurance that our small sample of patients is representative of the larger group.

The current study suggests that severe chronic alcoholism damages the central nervous system extensively, affecting not only specific regions of the cerebral cortex and cerebellum, but also the substantia nigra or its dopaminergic projections to the putamen or both. Nigrostriatal dopaminergic projections are specifically affected in Parkinson’s disease, and a recent study compared neuropsychological performance and here again observed no differences between the well-characterized alcoholic subjects studied previously and our current small sample investigated with DTBZ. The results provide assurance that our small sample of patients is representative of the larger group.

The current study suggests that severe chronic alcoholism damages the central nervous system extensively, affecting not only specific regions of the cerebral cortex and cerebellum, but also the substantia nigra or its dopaminergic projections to the putamen or both. Nigrostriatal dopaminergic projections are specifically affected in Parkinson’s disease, and a recent study determined quantitatively the intensity of the loss of VMAT2 in this disorder.58 That study used a racemic mixture (+) of DTBZ and reported specific binding, whereas the present study used the active (+) enantiomer and reported binding normalized to the cerebral cortex. The two sets of data can be compared by examining the ratio (DV − 1.0)patient/(DV − 1.0)control for the data in each study. In the current study, this yields a ratio of binding for alcoholic/control of 0.94 in the caudate nucleus and 0.87 in the putamen. Thus, in the alcoholic subjects examined in the present study, binding was reduced 6% in the caudate nucleus and 13% in the putamen. In the study of Parkinson’s disease,59 the ratio of binding for patient/control was 0.57 in the caudate nucleus and 0.39 in the putamen, indicating estimated reductions of 43% in the caudate nucleus and 61% in the putamen. Although the changes in the alcoholic subjects are much less than those in Parkinson’s disease and hence insufficient to cause clinically symptomatic parkinsonism, the reductions could result in subtle disorders of motor control and predispose to the development of parkinsonism. Indeed, one study has suggested an association between alcoholism and parkinsonism.60 At present, alcoholism is not known to be a risk factor for Parkinson’s disease, although this could reflect the limited life span of many severe chronic alcoholics and the older age of symptomatic onset in most patients with Parkinson’s disease.

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