Decreased cerebral blood flow of the right anterior cingulate cortex in long-term and short-term abstinent methamphetamine users

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Abstract

Background: The aim of the current study was to explore changes of relative regional cerebral blood flow (rCBF) in long-term and short-term abstinent methamphetamine (MA) users.

Methods: Relative rCBF in 40 abstinent MA users and 23 healthy comparison subjects was compared by the technetium-99m-hexamethyl-propylene amine oxime (99mTc-HMPAO) single photon emission computed tomography (SPECT). Relative rCBF in areas that were found to differ significantly was also compared in groups of MA users with short-term (<6 months) and long-term (≥6 months) abstinence.

Results: MA users showed decreased relative rCBF in the right anterior cingulate cortex (Brodmann area 32) relative to healthy comparison subjects. Long-term abstinent MA users had significantly greater rCBF than short-term abstinent MA users.

Conclusions: We report that abstinent MA users have decreased rCBF in the anterior cingulate cortex with smaller relative decreases in subjects with prolonged abstinence.

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Keywords: Methamphetamine; Single photon emission computed tomography; Cerebral blood flow; Anterior cingulate; Abstinence

1. Introduction

Methamphetamine (MA) has been reported to cause long-term damage on dopaminergic neurons of human (Wilson et al., 1996) and animal (Preston et al., 1985). Being closely associated with dopaminergic system, basal ganglia are more vulnerable to neurotoxic effects of the MA than other brain areas (Volkow et al., 2001a,b,d; Sekine et al., 2003). Prior brain imaging studies have also reported that MA users had abnormal glucose metabolism and decreased dopamine transporter level, especially in striatum and frontal cortices (Volkow et al., 2001a,b,d; Sekine et al., 2003; London et al., 2004).

Perfusion deficits and relative perfusion decreases have also been reported in MA users (Iyo et al., 1997; Chang et al., 2002). Iyo et al. (1997) have found multiple focal perfusion deficits in frontal cortices of six of nine abstinent MA users on qualitative reading of the technetium-99m-hexamethyl-propylene amine oxime (99mTc-HMPAO) single photon emission computed tomography (SPECT). 99mTc-HMPAO is a lipophilic radioactive tracer which crosses the blood–brain barrier easily and uptake of this tracer in the brain depends on the cerebral blood flow (Netrincek et al., 1987). Chang et al. (2002) have reported, in a perfusion magnetic resonance (MR) imaging study, a decrease of the relative regional cerebral blood flows (rCBF) in frontal cortex and basal ganglia of MA users, relative to healthy comparison subjects. Perfusion MR measures...
Table 1. Demographic and clinical characteristics of methamphetamine users and healthy comparisons

<table>
<thead>
<tr>
<th></th>
<th>Healthy comparison group (n=23)</th>
<th>Methamphetamine user group (n=40)</th>
<th>Short-term abstinence (n=13)</th>
<th>Long-term abstinence (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.0 ± 6.3</td>
<td>35.3 ± 6.3</td>
<td>34.5 ± 6.4</td>
<td>34.3 ± 6.1</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>16/7</td>
<td>32/8</td>
<td>12/1</td>
<td>20/7</td>
</tr>
<tr>
<td>Total cumulative MA dose (g)</td>
<td>322 ± 428.4</td>
<td>431.7 ± 699.4</td>
<td>268.4 ± 242.1</td>
<td></td>
</tr>
<tr>
<td>Average daily MA dose (g)</td>
<td>0.56 ± 0.43</td>
<td>0.74 ± 0.41</td>
<td>0.40 ± 0.41</td>
<td></td>
</tr>
<tr>
<td>Abstinence period (months)</td>
<td>24.9 ± 36.1</td>
<td>2.7 ± 1.7</td>
<td>35.7 ± 40.0</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption in 30 days before test (unit/month)</td>
<td>2.6 ± 4.0</td>
<td>10.7 ± 21.9</td>
<td>12.4 ± 31.1</td>
<td>9.9 ± 16.5</td>
</tr>
<tr>
<td>Smoking (pack-year)</td>
<td>4.1 ± 8.4</td>
<td>10.0 ± 12.9</td>
<td>9.1 ± 16.5</td>
<td>10.4 ± 11.1</td>
</tr>
</tbody>
</table>

The blood flow in small capillaries and large vessels using the signal changes caused by the contrast agent during its first pass through the blood vessels in the brain (Rosen et al., 1989). However, there has been no prior quantitative 99mTc-HMPAO SPECT study of MA users.

Functional changes induced by the MA use may be affected by the length of the abstinence period (Volkow et al., 2001c; Wang et al., 2004). After long-term (>1 year) abstinence period, the recovery of dopamine transporter levels in striatum as measured by positron emission tomography (PET) imaging with dopamine transporter-specific radioligand ([125I-d-threo-methylphenidate] (Volkow et al., 2001c) and the recovery of glucose metabolism in thalamus as assessed by PET imaging with fluorodeoxyglucose which is absorbed into the brain parenchyma like glucose but is not metabolized (Wang et al., 2004) have been reported. In our recently completed study, long-term abstinence (≥6 months) MA users had significantly greater prefrontal gray matter density than short-term abstinence (<6 months) MA users, but lesser than healthy comparison subjects (Kim et al., in press). Iyo et al. (1997) have reported that four of five long-term abstinent MA users (abstinence periods ≥5 years) had also perfusion deficits on qualitative readings. However, there has been no prior study comparing the difference of the relative CBF between long-term abstinent MA users and short-term abstinent MA users.

Based on prior imaging studies suggesting abnormalities in frontal or subcortical cortices, we hypothesized that abstinent MA users would have decreased relative CBF in these areas, as measured by 99mTc-HMPAO SPECT. We also hypothesized that, in accord with previous reports of functional and structural recovery with abstinence, long-term abstinent MA users would have a lesser decrease of relative CBF than short-term abstinent MA users.

2. Methods and materials

2.1. Subjects

Inclusion criteria were: (1) ages: 19–49 years, (2) DSM-IV methamphetamine abuse or dependence as determined by Structured Clinical Interview for DSM-IV (SCID-IV), as administered by experienced psychiatrists (3) abstinence period ≥4 weeks and (4) cumulative intravenous MA use over 50.0 g. Exclusion criteria were: (1) current or past any significant medical or neurological illness, (2) current or past history of axis I psychiatric disorder of schizophrenia, bipolar disorder and other psychotic disorders, and any current axis I disorder requiring psychotropic medications, as identified by SCID-IV, (3) anti-social or borderline personality disorders, as identified by the Personality Disorder Questionnaire-4, (4) lifetime exposure to any other substances except nicotine, caffeine, or social drinking of alcohol and (5) contraindications to magnetic resonance scanning.

Forty MA users and 23 healthy comparison subjects were recruited through advertisements at local newspapers and at the Korean Association against Drug Abuse. Study protocol was approved by the Institutional Review Boards at Seoul National University Hospital and McLean Hospital, MA, USA. After complete description of the study to the subjects, written informed consent was obtained.

There were no significant differences in age, sex and parents’ socioeconomic status between 40 abstinent MA users (32 men and 8 women, 35.3 ± 6.3 years) and 23 healthy comparison subjects (16 men and 7 women, 33.0 ± 6.3 years). Although depressive or anxiety disorders were not in the exclusion criteria, there was no comorbid categorical DSM-IV diagnosis of depressive or anxiety disorders in both groups. All MA users were intravenous users. Total cumulative and average daily doses were 322.0 ± 428.4 and 0.58 ± 0.43 g, respectively. Mean abstinence period of the MA users was 24.9 ± 36.1 months.

In accord with previous studies (Volkow et al., 2001c; Wang et al., 2004; Kim et al., in press), MA users were categorized into short-term (<6 months) abstinent users (12 men and 1 woman, 37.5 ± 6.4 years) and long-term (≥6 months) abstinent users (20 men and 7 women, 34.3 ± 6.1 years). There were no significant differences in age, sex, parents’ socioeconomic status, the total cumulative and average daily dose between these two MA user groups. There were no significant differences in alcohol and cigarette use variables between MA and healthy comparison groups and between long-term and short-term abstinence MA subgroups. Detailed characteristics are presented in Table 1.
2.2. Acquisition of single photon emission computed tomography

555 MBq $^{99m}$Tc-HMPAO was administered and the SPECT image was acquired using a tri-head gamma camera (Prism 3000; Picker International, Cleveland, OH, USA). The energy window was set at 140 keV with a 15% width. The resolution of a point source in water for the SPECT camera is 10 mm. One hundred and twenty frames were acquired, in the step and shoot mod, with each frame acquired for 20 s. Frames were 128 $\times$ 128 pixels in size, transaxial images were reconstructed as 64 $\times$ 64 matrices and filtered with a Metz filter ($x = 1.5–2.0$). Finally, 40–50 images from the top of the cerebral cortex to the bottom of the cerebellum perpendicular to the orbito-meatal line were reconstructed.

2.3. Statistical analysis

Statistical parametric mapping 99 (SPM) (Friston et al., 1991) was used to determine the difference of relative rCBF in $^{99m}$Tc-HMPAO SPECT images between MA users and healthy comparison subjects. All the images were spatially normalized to remove inter-subject anatomical variability using a template provided by SPM (Friston et al., 1991). Spatially normalized images were smoothed by convolution using an isotropic Gaussian kernel with 12-mm FWHM. The count of each voxel was normalized versus the total count for the brain (proportional scaling) to remove the effects of the global CBF differences of each individual. After spatial and count normalization, significant differences of rCBF between MA users and healthy comparison subjects were estimated at every voxel using $t$-statistics. Parameters to define regions of significant differences were conservatively set. These include $p$-value = 0.05 (corrected for multiple comparisons), height threshold $t = 4.86$ and the extent threshold = 50 voxels. For volume of interest (VOI) count analysis on the significantly different voxel cluster, normalized counts were calculated using VOI module of SPM.

Group differences in variables involving continuous data were computed using independent $t$-tests and ANOVA with Tukey’s HSD post hoc tests. Between-group comparisons involving categorical data were assessed using Fisher’s exact test for $2 \times 2$ table. Statistical significance was defined at the 0.05 and two-tailed. Stata 7.0 for Windows was used for computations.

3. Results

There were significant decreases in relative rCBF in the right anterior cingulate cortex (Talairach coordinates $[x, y, z]$: 6, 36, 24; Brodmann area 32, 5.2% decrease) in MA users relative to healthy comparison subjects (corrected $p < 0.05$, $t > 4.86$) (Fig. 1). For the relative rCBF in the area of significant difference, there were significant group differences between three groups (ANOVA, $F = 23.2$, d.f. = 2, 60, $p < 0.01$; short-term abstinent MA users < long-term abstinent MA users < healthy comparison subjects, by Tukey’s HSD post hoc tests) (Fig. 2).

Long-term MA abstinent users had greater relative rCBF in the right anterior cingulate cortex than short-term MA abstinent users. In addition, we have conducted additional sets of analyses to test correlations between clinical variables (length of abstinence, duration and total amount of methamphetamine use and age), as continuous variables and relative rCBF in all MA users. However, there were no significant correlations between these clinical variables and relative rCBF in the right anterior cingulate cortex.

4. Discussion

We report a decreased relative rCBF in the right anterior cingulate cortex in MA users, with smaller relative decreases in subjects with prolonged abstinence. To the best of our knowledge, the current report is the first quantitative $^{99m}$Tc-HMPAO SPECT study in MA users. Furthermore, we compared the rCBF of short-term and long-term abstinent MA users. Strengths of our study include: (1) all MA subjects were without comorbid axis I or II disorders, for which structural brain deficits have been reported, (2) all MA subjects were not only without current or lifetime diagnosis of other substance abuse/dependence but...
and McFarland, 2003). The anterior cingulate cortex is also suggested to converge on the anterior cingulate cortices (Kalivas cue-, drug- and stress-related reinstatement) have been suggested types of reinstatements of drug-seeking behaviors (i.e. dependence (Goldstein and Volkow, 2002). In addition, all dissociated with craving and compulsive drug administration in drug dependence (Goldstein and Volkow, 2002). In conclusion, we report that abstinent MA users have decreased relative rCBF in the right anterior cingulate cortex. As the anterior cingulate cortex has the highest density of dopamine fibers among human cortices (Paus, 2001), perfusion decreases in the right anterior cingulate may be mediated by the neurotoxic effects of MA to the dopaminergic neurons.

Our findings of relative perfusion decreases in the right anterior cingulate cortex is also in line with other prior imaging studies reporting that MA users had the decreased gray matter density (Thompson et al., 2004), the glucose hypometabolism (Kim et al., in press). It also echoes recent reports that levels of dopamine transporter in striatum and decreased glucose metabolism in thalamus recover after abstinence periods of 12–17 months (Volkow et al., 2001c; Wang et al., 2004). These findings suggest that the recovery of relative perfusion decreases may occur with long-term abstinence. However, in the present study, rCBF in long-term abstinent MA users was lower than that of healthy comparison subjects. Therefore, despite the recovery with long-term abstinence, perfusion deficits may be a long-lasting sequel of MA use.

Another possible explanation can be suggested for rCBF differences between short-term and long-term MA user groups. MA users with the higher rCBF in the anterior cingulate may have the preceding (i.e. before MA exposure) constitutions more capable of maintaining the abstinence than MA users with the lower rCBF. However, there were no significant differences between two MA groups in cumulative doses, average daily doses and durations of MA use, which may be closely related with abstinence and relapse of MA use. Therefore, the recovery of rCBF with long-term abstinence is a more plausible explanation for rCBF differences between two MA groups than differences in the preceding constitution to maintain abstinence.

In conclusion, we report that abstinent MA users have decreased relative rCBF in the right anterior cingulate cortex, and that individuals who abstain from MA use for more than 6 months have smaller relative perfusion decreases than more recent MA users.

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References


