Dopamine transporter dysfunction in Han Chinese people with chronic methamphetamine dependence after a short-term abstinence

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Emission-computed single-photon emission-computed tomography (SPECT) after the administration of \textsuperscript{99mTc}-TRODAT-1 was performed on healthy subjects and subjects with methamphetamine (METH) dependence at time 1 (T1) after 24–48 h of abstinence, time 2 (T2) after 2 weeks of abstinence, and time 3 (T3) after 4 weeks of abstinence. In contrast to values in controls, the values of the striatal DAT specific uptake ratios (SURs) in subjects with METH dependence were significantly lower at T1 (n=25), T2 (n=9), and T3 (n=8); a mild increase in SURs was observed at T2 and T3, but values were still significantly lower than those in controls. In subjects with METH dependence, there was a trend for a negative correlation of striatal DAT SURs and craving for METH at T1. METH craving, anxiety and depression scores significantly decreased from T1 to T2 to T3. We conclude that Han Chinese people with METH dependence experience significant striatal DAT dysfunction, and that these changes may be mildly reversible after 4 weeks of abstinence, but that DAT levels still remain significantly lower than those in healthy subjects. The mild recovery of striatal DAT may parallel improvements in craving, anxiety and depression.

\textbf{A B S T R A C T}

1. Introduction

People throughout the world are afflicted with the abuse of or dependence on N-methyl-phenylpropylamine, methamphetamine (METH), and other related substances. North America, East and South-East Asia, Europe, and Oceania have witnessed an increase in the number of clandestine laboratories set up to manufacture METH (United Nations Office on Drugs and Crime (UNODC), 2010). Additionally, METH abuse is an increasingly common disorder in China and other countries in East Asia. In contrast to 2005, the number of METH abusers increased by 31.4% in China in 2009. Characterization of the pathophysiology of METH addiction will foster the development of effective interventions to combat a worldwide scourge.

METH, a highly addictive central nervous system stimulant (Abdul et al., 2011), is toxic to dopamine neuron terminals in the central nervous system. METH promotes the release of dopamine and inhibits the reuptake of dopamine. Striatal dopamine transporter (DAT) activity decreases in mice treated with METH (Sandoval et al., 2000). METH destroys the dopamine terminals in the striatum in several animal species (Kogan et al., 1976). DAT, a transmembrane protein that mediates the reuptake of dopamine (DA), regulates the actions of intrasynaptic and extrasynaptic DA in the brain. DAT plays a major role in modulating dopaminergic neurotransmission by rapid reuptake of released dopamine into presynaptic terminals and regulation of reward and dependence in drug addiction (Volkow et al., 1997). METH acts to increase the release of DA from the vesicles of presynaptic DA terminals leading to an increase of DA in the synaptic cleft. Chronic drug administration produces compensatory changes, such as reduction of DAT, which could affect drug-seeking behavior (Wang et al., 2008). Humans who abuse METH demonstrate reductions of DAT and motor and cognitive deficits (Volkow et al., 2001; McCann et al., 2008).

The reductions in striatal DAT activity in those who abuse METH likely produce the tolerance to METH experienced by METH abusers and that lead to the characteristic incessant dose escalations (Woolverton et al., 1989; Wilson et al., 1996). Therefore, DAT plays a vital role in METH addiction.

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Although the acute reduction of striatal DAT in people dependent on METH resolves after 12–17 months of abstinence from METH, poor memory and slow motor performance persist as chronic deficits (Volkow et al., 2001). The marked acute reduction in presynaptic striatal dopamine function of vervet monkeys after the parenteral administration of METH subsided after 32 weeks of abstinence (Melega et al., 1997). After 2 weeks of abstinence from METH, people with METH dependence demonstrated a partial recovery in levels of striatal DAT (Chou et al., 2007).

We hypothesize that during abstinence people with METH dependence will experience amelioration of striatal DAT dysfunction along with a reduction of anxiety, depression, and craving for METH. The purpose of this study is to assess the time course of DAT levels in Han Chinese subjects with METH dependence after brief abstinence. Previous studies have found that ethnic origin might be associated with the gene–personality interactions. Therefore, genetic heterogeneity was controlled for in this study by recruiting only Han Chinese individuals (Noblett and Coccaro, 2005). In this study we used single photon emission computed tomography (SPECT) with [2][2-[[3-[(4-Chlorophenyl)-8-methyl-8-azabicyclo[3.2.1]-oct-2-yl]-methyl][2-mercaptoethyl] amino]ethyl][amino]ethanethiolato(3-)]-[99mTc]-technetium ([99mTc-TRODAT-1]) to assess DAT levels in healthy control subjects and subjects with METH dependence.

2. Methods

2.1. Participants

Healthy participants comprised 25 normal control subjects (15 men and 10 women; 32 ± 7.6 years old, range 19–43 years) in good general health. Subjects were excluded for a past or present history of drug abuse and other diseases. In addition, 25 subjects dependent on METH (17 men and 8 women; 30.6 ± 5.5 years old, range 21–41 years) were recruited from the Drug Rehabilitation Centre. They underwent physiological detoxification and were not taking medications to control craving or withdrawal symptoms. Table 1 characterizes their METH abuse histories. Inclusion criteria were the presence of a lifetime history of METH abuse histories. Inclusion criteria were the presence of a lifetime history of METH dependence and the degree of craving in T1. Friedman’s test was used to compare METH craving was measured by using a 10-point visual analog scale (VAS) where 0 was anchored at “not at all” and 10 was anchored at “extremely high”, and subjects rated their “desire to use METH” along this scale (Sinha et al., 2000). Anxiety and depression were measured by the Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D) (Reijnders et al., 2010). We administered these evaluations to METH abusers at T1, T2, and T3.

2.2. Craving, anxiety and depression evaluation

METH craving was measured by using a 10-point visual analog scale (VAS) where 0 was anchored at “not at all” and 10 was anchored at “extremely high”, and subjects rated their “desire to use METH” along this scale (Sinha et al., 2000). Anxiety and depression were measured by the Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D) (Reijnders et al., 2010). We administered these evaluations to METH abusers at T1, T2, and T3.

2.3. Imaging the density and the distribution of the dopamine transporter (DAT) in the brain

The radiotracer [99mTc-TRODAT-1 was synthesized from 99mTc-O4− (GMS Pharmaceutical Co. Ltd., Shanghai, China) and the TRODAT-1 ligand (the Institute of Wuxi National Atomic Energy Research, Jiangsu Province, China) as described previously with minor modifications (Kung et al., 1997) attaining radiochemical purity greater than 96%. SPECT was performed by using high resolution fan beam collimators of a Siemens NIMECAM Gauntly Dual Head Ex. Base (Siemens, Erlangen, Germany). Dynamic scans were started between 120 and 180 min after the intravenous injection of 740 to 925 MBq (20–25 mCi) of 99mTc-TRODAT-1 (Liu et al., 2010; Schmitt et al., 2005). The SPECT images were acquired in a 128 × 128 matrix with a 1.0 zoom over a circular 360° rotation (180° for each head). Transverse images were reconstructed using a Metz filter with a cut-off of 0.55 Nyquist and an order of 15. An attenuation coefficient of m = 0.12 cm was used according to Chang’s first-order method (Chang, 1995). The transverse image thickness was 0.39 cm (1 pixel).

2.4. Image analysis

Regions of interest (ROIs) were drawn manually on the subregions of both striatal and occipital areas using individual MRI scans as a reference (non-registered) on SPECT scans by an experienced nuclear medicine specialist unaware of the histories of the participants (Yeh et al., 2012). Standardized uptake ratios (SURs) were assessed bilaterally on the ROIs in the four consecutive transverse slices with highest radioactivity. The arithmetic mean of these four slices was calculated. The occipital cortices (OC) were also drawn in the same way in two consecutive transverse slices and served as the reference region. In the study, an equilibrium-ratio analysis was chosen to calculate the DAT SURs. The SUR was calculated by subtracting the mean counts per pixel in the OC from the mean counts per pixel in the striatum and by dividing the result by the mean counts per pixel in the OC as follows: SUR = [OC – (target – OC)/OC, where the target represents right striatum and left striatum, respectively.

2.5. Statistics

Analysis of variance (ANOVA) was performed to contrast subjects with METH dependence with healthy normal control subjects. Post hoc t tests were done to assess the differences that were significant. Analysis of repeated measures one-way ANOVA (RM-ANOVA) was used to compare the SURs in subjects with METH dependence at T1, T2, and T3, followed by Least Significant Difference (LSD) post-hoc tests. Pearson’s correlation coefficient was used to compare the correlation of SUR and the degree of craving in T1. Friedman’s test was used to compare METH craving, anxiety, and depression ratings at T1, T2, and T3. Equality of variances was tested using Levene’s test of the equality of variances. All tests were two-tailed, and significance was set at P < 0.05. Results were reported as the mean ± S.D. All statistics were performed using SPSS 15.0 software.

3. Results

3.1. Participants

SPECT imaging was performed at T1 in 25 healthy subjects and 25 subjects with METH dependence at T1. At T2, 16 METH users dropped out of the study, and 17 METH users dropped out at T3. Ultimately, eight subjects with METH dependence completed three scans in this study.

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3.2. DAT in healthy controls and METH-dependent subjects

Comparison of SURs among healthy controls (n=25) and subjects with METH dependence at T1 (n=25), T2 (n=9) and T3 (n=8) showed a significant group effect in right striatum (F=24.46; d.f.=3,63; P<0.001) and in left striatum (F=21.32; d.f.=3,63; P<0.001). Fig. 1 shows the SURs for the individual healthy control subjects and METH abusers at T1, T2, and T3. Post hoc t tests showed SURs in METH abusers at T1 were significantly lower than SURs in healthy controls in right striatum (1.23 ± 0.33 vs. 1.93 ± 0.28, P<0.001) and left striatum (1.24 ± 0.31 vs. 1.90 ± 0.28, P<0.001). There were also no differences between METH abusers and healthy control subjects at T2 and T3 (1.24 ± 0.31 vs. 1.41 ± 0.36, P<0.001) and left striatum (1.90 ± 0.28 and 1.36 ± 0.39, P<0.001).

3.3. DAT in METH-dependent subjects in T1, T2 and T3

Repeated measures (RM)-ANOVA was used to compare the SURs in the METH-dependent subjects who completed three scans. RM-ANOVA of SURs demonstrated a nonsignificant group by time interaction in the right striatum (F=0.894; P=0.446) and the left striatum (F=0.812; P=0.478). LSD post hoc t tests showed SURs were not significantly increased between METH abusers at T1 and T2 in the right striatum (P>0.05) and the left striatum (P>0.05). No differences were found between METH abusers at T2 and T3 in the right striatum (P>0.05) and the left striatum (P>0.05). There were also no differences between METH abusers at T1 and T3 in the right striatum (P>0.05) and the left striatum (P>0.05).

3.4. Neuropsychological performance and clinical ratings in METH-dependent subjects at T1, T2 and T3

There was a low negative correlation between SURs and the scores of METH craving at T1 in (a) right striatum (1.23 ± 0.33 and 3.96 ± 1.97, r = -0.398, P=0.049). No obvious correlation was found in (b) left striatum (1.24 ± 0.31 and 3.96 ± 1.97, r = -0.323, P=0.116), as shown in Fig. 3.

Performance in neuropsychological testing showed a significant trend toward improvement in METH abusers at T1, T2 and T3. The craving scores of subjects with METH dependence at T1, T2, and T3 (3.96 ± 1.97, 3.56 ± 1.01, and 1.88 ± 1.55; Friedman test, \( \chi^2 = 17.64 \), P<0.01) were increased. There was significant improvement in the anxiety (HAMA) scores of subjects with METH dependence at T1, T2, and T3 (21.36 ± 10.55, 19.89 ± 11.11 and 15.38 ± 7.21; Friedman test, \( \chi^2 = 25.00 \), P<0.01). There were significant differences in the depression (HAMD) scores of subjects with METH dependence at T1, T2, and T3 (15.92 ± 8.24, 13.56 ± 4.12 and 12.13 ± 8.71; Friedman test, \( \chi^2 = 25.00 \), P<0.01). Fig. 4 shows the craving (A), anxiety (HAMA) scores (B), and depression (HAMD) scores (C) of subjects with METH dependence at T1, T2, and T3.

4. Discussion

This Han Chinese study documented a significant DAT reduction in subjects with METH dependence relative to healthy normal comparison subjects. Our findings in the Han Chinese population are consistent with the previous reports in animal, post-mortem and living human populations (McCann et al., 1998; McCann et al., 2008; Sandoval et al., 2000; Villemagne et al., 1998).

Neuromaging techniques, including positron emission tomography (PET) and SPECT, have been used to evaluate the levels of striatal DAT and amygdalar serotonin transporter in populations of subjects with drug addiction. Striatal DAT levels were significantly reduced on PET in baboons and abstinent human subjects with METH dependence after the administration of \([^{13}C]\)WIN35428 (McCann et al., 1998; Villemagne et al., 1998).

Han Chinese People with intermittent abuse of METH for several years demonstrated a partial recovery in striatal DAT SUR.
after 2 weeks of abstinence from METH (Chou et al., 2007). In our study, however, DAT dysfunction showed a slight tendency toward normalization, but there was no significant difference in the striatal DAT of subjects dependent on METH after abstinence from METH as long as 4 weeks.

Chou et al. (2007) studied people with intermittent abuse of METH who showed a recovery of striatal DAT function after only 2 weeks of abstinence. The one participant with continuous use of METH for 12 years in the study of Chou et al. (2007) likely had METH dependence. This man with apparent METH dependence demonstrated a striking recovery in DAT function after 2 weeks’ abstinence from METH. He was younger than most of the participants with METH dependence in the current study. The striking recovery in striatal DAT function of the participants who abused METH is the study of Chou et al. (2007) may be explained by their youth and their intermittent abuse of METH. By contrast, the participants with METH dependence in the current study are more than a decade older than the participants in the study of Chou et al. (2007). By extrapolation, the resilience of youth to the striatal dopamine dysfunction after abuse of METH (Chou et al., 2007) evidently disappears after a mere decade increase in age. METH dependence results in permanent damage to striatal DAT function.

The severity of psychiatric symptoms was proportional to the reduction of striatal DAT of people who used METH (Sekine et al., 2001). During the first day or two of withdrawal from METH at T1, the subjects with METH dependence in the current study exhibited craving for METH that was inversely correlated with striatal DAT SURs (Fig. 3). The reduction of striatal DAT can enhance drug craving, and craving for addictive drugs may predict drug-seeking behavior and relapse in abstinent individuals with drug dependence (Hartz et al., 2001). The METH craving level in acute abstinence may be attributed to the loss of striatal DAT.

Physiological dependence on METH has variable associations with craving and other symptoms of drug use (Newton et al., 2009). The time course of craving, anxiety and depression in subjects with METH dependence is variable (Fig. 4). Depressive symptoms play a role in impulsive drug-seeking behavior (Hartz et al., 2001). Chronic drug abuse induces anxiety symptoms (Anthony et al., 1989). Craving for METH (Sinha et al., 2000), anxiety scores and depression scores decrease (Reijnders et al., 2010) with increasing time of abstinence from METH (Fig. 4).

People with METH dependence who exhibit high impulsivity also experience high craving for METH (Tziortzis et al., 2011). People with high impulsivity report more pleasure in response to amphetamine. Thus, impulsivity constitutes a crucial variable to measure in future studies of dependence on METH and other substances.

Limitations of the current study include the small sample size. Further studies with larger sample sizes are necessary. While abstinence produced a partial recovery of striatal DAT function in a Han Chinese population of young adults (Chou et al., 2007), minimal recovery occurred with abstinence in the older Han Chinese group of subjects with METH dependence in the current study. Future studies with stratified populations across the life-span are needed to characterize the alterations in DAT function with age in health and in METH dependence. Further studies with larger populations of other ethnic groups of METH abusers are needed to assess the abnormalities in DAT in METH addiction in short-term and long-term abstinence. Impulsivity is a personality characteristic that is important in understanding METH use. Further study should measure impulsivity in attempts to intervene in METH abuse. The 99mTc-TRODAT-1 ligand has the advantage of being relatively inexpensive and available. However, its specific signal is lower than that of 123I-based SPECT tracers and SPECT measures accordingly have lower resolution PET (Shen et al., 2011).
Since both the noradrenergic and the dopaminergic systems likely play a role in the physiological and psychological effects of stimulants, characterization of the pathophysiology of withdrawal from METH should include measurement of both noradrenergic and dopaminergic effects. Since memory deficits are associated with decreased striatal DAT function in people who use METH (McCann et al., 2008), the measurement of memory function sequentially in the course of withdrawal from METH will be informative.

We conclude that in Han Chinese populations, striatal DAT function was significantly decreased in subjects with METH dependence in contrast to healthy normal control subjects. The loss of DAT in METH-dependent subjects may be partially counteracted after a short-term abstinence.

Cring for METH, anxiety and depressive symptoms peaked after 1–2 days of abstinence from METH before diminishing in intensity after 2 weeks of METH abstinence in this population of Han Chinese with METH dependence. Recognition of this time course of craving, anxiety and depressive symptoms would allow clinicians to a likely increase in craving, anxiety and depressive symptoms during the first 2 days of withdrawal from METH. These findings will provide the bases for the development of effective treatment plans for people with METH dependence as they withdraw from substances. Vigilance by clinicians for the risk of relapse during the first 2 days of METH abstinence is crucial to the prevention of repeated use of METH.

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