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Decreased frontal lobe phosphocreatine levels in methamphetamine users☆

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ABSTRACT

Background: Mitochondria-related mechanisms have been suggested to mediate methamphetamine (METH) toxicity. However, changes in brain energetics associated with high-energy phosphate metabolism have not been investigated in METH users. Phosphorus-31 (^{31}P) magnetic resonance spectroscopy (MRS) was used to evaluate changes in mitochondrial high energy phosphates, including phosphocreatine (PCr) and β-nucleoside triphosphate (β-NTP, primarily ATP in brain) levels. We hypothesized that METH users would have decreased high-energy PCr levels in the frontal gray matter.

Methods: Study participants consisted of 51 METH (age = 32.8 ± 6.7) and 23 healthy comparison (age = 31.1 ± 7.5) subjects. High-energy phosphate metabolite levels were compared between the groups and potential gender differences were explored.

Results: METH users had lower ratios of PCr to total pool of exchangeable phosphate (PCr/TPP) in the frontal lobe as compared to the healthy subjects ($p = .001$). The lower PCr levels in METH subjects were significantly associated with lifetime amount of METH use ($p = .003$). A sub-analysis for gender differences revealed that female METH users, who had lower daily amounts (1.1 ± 1.0 g) of METH use than males (1.4 ± 1.7 g), had significantly lower PCr/TPP ratios than male METH users, controlling for the amount of METH use ($p = .02$).

Conclusions: The present findings suggest that METH compromises frontal lobe high-energy phosphate metabolism in a dose-responsive manner. Our findings also suggest that the abnormality in frontal lobe high-energy phosphate metabolism might be more prominent in female than in male METH users. This is significant as decreased PCr levels have been associated with depressive symptoms, and poor responses to antidepressant treatment have been reported in those with decreased PCr levels.

1. Introduction

Methamphetamine (METH) abuse is a disorder characterized by compulsive METH-craving and consumption despite an apparent awareness of serious negative consequences. METH use has been linked to the emergence of psychotic symptoms (Iyo et al., 2004; London et al., 2004; Winslow et al., 2007) as well as morphological, functional, and neurochemical abnormalities in multiple brain areas (Bae et al., 2006; Chung et al., 2007; Ernst et al., 2000; Hwang et al., 2006; Oh et al., 2005). Alterations in monoaminergic neurotransmission (Kokoshka et al., 1998; Ricaurte et al., 1980; Robinson and Berridge, 1993) in the frontal lobe have been related to cognitive impairments in METH users because prefrontal cortical neural networks play a central role in impaired decision-making and inhibitory control (Lubman et al., 2004; Yucel and Lubman, 2007).

In METH toxicity, multiple lines of evidence suggest that dysfunctional energy metabolism plays an important role. For instance, (1) impairments of mitochondrial function have been reported after administration of METH to animals including impairments in mitochondrial electron transport chain enzyme complexes (Brown et al., 2005; Burrows et al., 2000a; Klongpanichapak et al., 2006); (2) METH toxicity involves a depletion of energy stores, evidenced by synergistic metabolic inhibition by METH resulting in depletion of striatal dopamine content (Burrows et al., 2000b); and (3) ex vivo METH exposure has been associated with oxidative cell injury

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and apoptosis in rat cortical neuron and undifferentiated pheochromocytoma (PC12) cells (Cunha-Oliveira et al., 2006; Oliveira et al., 2002). Considering the evidence for mitochondrial involvement in the potential pathophysiology of METH toxicity, it is not surprising that proton (^{1}H) magnetic resonance spectroscopy (MRS) studies have consistently reported that METH users, relative to healthy comparison subjects, have decreased levels of total creatine (phosphocreatine plus creatine) as well as decreased N-acetylaspartate (NAA, a marker of neuronal viability or integrity (Moffett et al., 2007)) levels (Chang et al., 2005; Ernst et al., 2000; Nordahl et al., 2002; Sailasuta et al., 2010b; Sekine et al., 2002; Smith et al., 2001; Sung et al., 2007; Taylor et al., 2007). As NAA synthesis occurs primarily in the mitochondria (Patel and Clark, 1979), decreased NAA levels in METH users are potentially consistent with compromised brain energetics.

Phosphocreatine (PCr) and adenosine triphosphate (ATP) make up the PCr–ATP energy buffering system in neuronal cells that have high and fluctuating energy demands. The enzyme creatine kinase controls the transfer of a phosphate group from PCr to ADP, thereby replenishing brain ATP. It is reported that PCr serves as a buffer to maintain constant ATP levels so that ATP levels remain relatively stable at the cost of PCr expenditure (Schlattner et al., 2006). In the fluctuating energy requirements of neurons, mitochondrial dysfunction may lead to decreased formation of phosphocreatine mediated by the mitochondrial creatine kinase isoenzyme (Dolder et al., 2001; Wallimann et al., 1998). Regarding region specific deficits, frontal hypometabolism has been reported in METH users using positron emission tomography (PET; Kim et al., 2005; London et al., 2004, 2005). These findings would be consistent with the potential mitochondrial abnormality and decreased PCr levels in the frontal lobe of METH users.

Published neuroimaging studies have reported gender differences in METH toxicity with favorable outcomes in female METH users in terms of frontal glucose metabolism and white matter hyperintensities/integrity (Bae et al., 2006; Chung et al., 2007; Kim et al., 2005), probably reflecting a protective effect of estrogen (Dhandapani and Brann, 2002). However, female psychostimulant users are more sensitive to the reinforcing effects than male users (Anker and Carroll, 2011; Carroll et al., 2004). Also, female METH users have a higher incidence of depression and more severe depressive symptoms than male METH users (Dluzen and Liu, 2008; Hser et al., 2005; Kalechstein et al., 2000). In non-METH users, depression severity has been significantly associated with decreased brain PCr levels (Kato et al., 1992), but it is not known what the effects of METH use will be on brain high energy phosphate metabolism in female METH users.

Phosphorus-31 (^{31}P)-MRS provides a unique method to evaluate changes in high-energy phosphate metabolites such as PCr and beta-nucleoside triphosphate (β-NTP), which arises primarily from ATP in brain (Renshaw et al., 2001). To date, there have been no reports measuring ^{31}P-MRS metabolite levels in METH users relative to healthy subjects. In this study, we aimed to investigate whether METH use significantly altered high energy phosphate metabolism. It was hypothesized that first, METH use would be associated with decreased high-energy PCr levels by ^{31}P-MRS in the frontal cortex, and second, that altered PCr levels will be significantly correlated with lifetime amount of METH use. In addition, we explored possible gender differences in the phosphorus metabolite levels in METH users.

2. Methods

2.1. Subjects

This was a cross-sectional study in which phosphorus MRS data was acquired to examine brain metabolite alterations related to METH use. The study participants consisted of 51 METH dependent subjects (age = 32.8 ± 6.7, female = 23) and 23 healthy comparison subjects (age = 31.1 ± 7.5, female = 11). Each individual underwent two dimensional phosphorus magnetic resonance spectroscopic imaging (2D ^{31}P-MRSI) as well as assessment of clinical and drug abuse history. METH-dependent subjects were evaluated for the severity of their lifetime METH use (METH amount, frequency, duration, and abstinence). Inclusion criteria for METH subjects were as follows: (1) age 18–55 years, (2) subjects who met diagnostic criteria for current methamphetamine abuse or dependence as their preferred drug of abuse as determined by the Structured Clinical Interview for DSM-IV (SCID-IV). A board certified psychiatrist took complete medical histories and physical examinations of the subjects. The SCID-IV was administered by a trained psychologist (ECM), and (3) METH use within the past six months. Exclusion criteria for METH subjects included: (1) major medical or neurological disorders, including HIV seropositivity; (2) comorbid psychiatric disorders including schizophrenia, bipolar disorder, and use of other illicit drugs as preferred drug of abuse; (3) major sensorimotor handicaps (e.g., deafness, blindness, and paralysis), full scale IQ < 70 or learning disabilities; and (4) contraindications to magnetic resonance imaging.

Healthy comparison (HC) subjects were recruited with the inclusion criteria (1) age 18–55 years, (2) no dependence or abuse of alcohol, METH, amphetamine, cocaine, heroin, alcohol, and cannabis, and (3) no psychiatric, neurologic, and medical disease identified by physical examination. The healthy subjects were matched on age and gender with METH users. The healthy subjects had a slightly higher level of education than METH users and this difference was controlled for statistically. Exclusion criteria for the HC subjects were the same as for the METH users. The study protocol was approved by the Institutional Review Boards of the University of Utah and the Department of Human Services of the State of Utah. Written informed consent was obtained from all study subjects before participation.

2.2. Magnetic resonance imaging and spectroscopy data acquisition and processing

2.2.1. Structural MR images. Brain MR imaging was performed using a 3 Tesla Siemens scanner (Trio, Siemens AG, Erlangen, Germany) and a ^{31}P/^{1}H double-tuned volume head coil (Clinical MR Solutions LLC, Brookfield, WI) for transmission and reception. To obtain high resolution T1-weighted anatomical images for tissue segmentation and positioning MRS grids, a three dimensional chemical Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) pulse sequence was used. The parameters for the structural MRI were as follows: T1 weighted image – TR = 2000 ms, TE = 3.37 ms, TI = 1100 ms, average number = 1, flip angle = 8°, FOV = 256 mm, matrix 256 × 192 × 144, bandwidth = 300 Hz/pixel, slice thickness 1.0 mm and no gap.

2.2.2. ^{31}P magnetic resonance spectroscopy. Phosphorus spectra were acquired on the same 3 Tesla Siemens system using the ^{31}P/^{1}H double-tuned volume head coil. The spectra were obtained using a two dimensional-chemical shift imaging (2D-CSI) free induction decay (FID) pulse sequence with TR = 3000, TE = 2.3 ms, average number = 36, flip angle = 90°, vector size = 1024, FOV = 200 mm × 200 mm, slice thickness = 2.5 cm, matrix 8 × 8, sampling bandwidth = 2.5 kHz, and voxel dimension = 2.5 cm × 2.5 cm. The 2D-CSI grid was positioned covering an axial brain slice just above an imaginary line connecting the anterior commissure and posterior commissure. The acquisition matrix of the 2D-CSI grid was 8 × 8 with the slice thickness 25 mm (Fig. 1). Shimming was performed over the excited brain volume. Since MRS data is significantly affected by magnetic field inhomogeneity, high order advanced shimming routine on the Siemens system was used to achieve linewidths of less than or equal to 15 Hz for the unsuppressed water signal. The proton channel was used for shimming, localization, and anatomic imaging. As an a priori region of interest (ROI), frontal lobe spectroscopic data were quantified. Also, as a control region for the comparison, temporoparietal lobe and occipital lobe were included in the spectroscopic and statistical analyses. The frontal lobe was selected as an active ROI because of prior reports suggesting frontal neurochemical abnormalities and hypometabolism in METH users (Kim et al., 2005; London et al., 2004, 2005; Sailasuta et al., 2010a).

2.2.3. ^{31}P-MRS data analysis. Before performing 2D fast Fourier transform (FFT) on raw data, a Hamming filter was applied to reduce the effect of the point-spread-function, and each free induction decay (FID) was line-broadened with 10 Hz of apodization. After Fourier transformation and frequency shift correction, zero-/first-order phase correction and baseline correction with polynomial interpolation were applied. Metabolite location error resulting from different chemical shift displacement was corrected along in-plane readout and phase-encoding directions. Following that, spatial filtering with a Hamming window function was implemented to reduce the signal contamination from neighboring voxels. The preprocessed ^{31}P-MRSI data was fitted using jMRUI software (Naressi et al., 2001) with the Advanced Method for Accurate, Robust and Efficient Spectral (AMARES) fitting algorithm (Vanhamme et al., 1997). Metabolites of interest were PCr, β-NTP, and their ratio (Fig. 1C). Each metabolite concentration was expressed relative to the total pool of exchangeable phosphate (TPP; Blumberg et al., 1999). Referencing ^{31}P metabolites to TPP facilitated effective evaluation of high energy phosphate metabolism (Amess et al., 1997; Cady et al., 2008; Iwata et al., 2008).

From the registered anatomical images, tissue segmentation was performed using FSL (FMRIB's Software Library) software so that cerebrospinal fluid (CSF)-corrected metabolite concentrations as well as gray matter percentage in each voxel