Available online at www.sciencedirect.com
ScienceDirect
Drug and Alcohol Dependence 88 (2007) 28–35
DRUG and ALCOHOL DEPENDENCE
www.elsevier.com/locate/drugalcdep

Relationship between *N*-acetyl-aspartate in gray and white matter of abstinent methamphetamine abusers and their history of drug abuse: A proton magnetic resonance spectroscopy study

Young Hoon Sung [a,b], Soo Churl Cho [a], Jaeuk Hwang [a], Seog Ju Kim [c], Hyungjun Kim [d], Sujin Bae [d], Namguk Kim [e], Kee Hyun Chang [f], Melissa Daniels [b], Perry F. Renshaw [b], In Kyoon Lyoo [a,b,d,*]

[a] *Department of Psychiatry, Seoul National University College of Medicine and Hospital, Seoul 110-744, Republic of Korea*
[b] *McLean Hospital Brain Imaging Center and Department of Psychiatry, Harvard Medical School, Belmont, MA 02478, USA*
[c] *Department of Psychiatry, Gachon Medical School, Incheon 405-760, Republic of Korea*
[d] *Interdisciplinary Program of Neuroscience, Seoul National University, Seoul 110-744, Republic of Korea*
[e] *Department of Industrial Engineering, Seoul National University, Seoul 110-744, Republic of Korea*
[f] *Department of Radiology, Seoul National University College of Medicine and Hospital, Seoul 110-744, Republic of Korea*

Received 22 February 2006; received in revised form 13 September 2006; accepted 14 September 2006

This study was presented at the 2004 College on Problems of Drug Dependence Annual Meeting that was held in San Juan, Puerto Rico on June 12–17, 2004.

Abstract

Objective: Altered concentrations of the brain metabolites, including *N*-acetyl-aspartate (NAA) and *myo*-inositol (MI), may indicate neurotoxicity associated with drug abuse. In this study, the authors explored differences in brain metabolites between abstinent methamphetamine (MA) abusers and healthy comparison subjects and the associations between metabolite concentrations and clinical characteristics.
Method: Proton magnetic resonance spectroscopy (MRS) was performed on 30 abstinent MA abusers and 20 healthy comparison subjects. Two sets of MA user subgroups were defined depending on abstinence duration (greater or less than 6 months) or the total cumulative MA dose (greater or less than 100 g lifetime). NAA and other metabolites were measured in the frontal gray and white matter and compared between MA abuser groups and healthy comparison subjects.
Results: MI concentrations were higher for the MA abusers relative to healthy comparison subjects. NAA concentration was lower in frontal white matter of MA abusers with a 'large' cumulative dose relative to those with a 'small' cumulative dose and to healthy comparison subjects. Additionally, in MA abusers NAA concentrations in frontal white matter correlated inversely with the cumulative MA dose. In contrast, there was no significant difference in frontal gray matter NAA concentration among the three groups. However, frontal gray matter NAA concentrations for MA abusers correlated negatively with the total cumulative MA dose and positively with the duration of abstinence. There were no differences between the different MA user groups for MI.
Conclusions: The current findings suggest that MA-induced metabolic alterations of frontal gray and white matter are dose-dependent, for primarily male subjects. Additionally, these findings potentially suggest that the MA-related abnormalities may, in part, recover with abstinence in gray matter, but not in the white matter regions.

Keywords: Methamphetamine; Magnetic resonance spectroscopy; Abstinence; *N*-Acetyl aspartate; Frontal lobe; Neurotoxicity

1. Introduction

Methamphetamine (MA) with its high addiction and abuse potential (Woolverton et al., 1984) has been shown to have toxic effects on dopamine nerve terminals in rodents (Cass and Manning, 1999; Friedman et al., 1998), non-human primates (Harvey et al., 2000; Melega et al., 1997) and humans (Volkow

* Corresponding author at: Department of Psychiatry, Seoul National University Hospital, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Republic of Korea. Tel.: +82 2 2072 3173; fax: +82 2 3672 0677.
E-mail address: inkylyoo@yahoo.com (I.K. Lyoo).

0376-8716/$ – see front matter © 2006 Published by Elsevier Ireland Ltd.
doi:10.1016/j.drugalcdep.2006.09.011

et al., 2001). It has also been shown to cause neuronal apoptosis (Deng and Cadet, 2000; Deng et al., 1999; Hirata and Cadet, 1997). In addition, neurons which are not related to dopamine, have been reported to be vulnerable to MA toxicity in vitro (Cadet et al., 1997; Yuan et al., 2001; Stumm et al., 1999). Since methamphetamine could induce degeneration of the dopamine nerve terminals and fibers (Ricaurte et al., 1984), abnormalities in white matter and gray matter regions of the brain in MA users may occur.

With its usefulness in measuring *in vivo* various chemical metabolites of human brain, magnetic resonance spectroscopy (MRS) has been increasingly used in psychiatric research (Lyoo and Renshaw, 2002). *N*-Acetyl-aspartate (NAA), a metabolite that can be measured using proton MRS, is considered a marker of neuronal viability (Urenjak et al., 1993) and consequently, may be a reliable candidate for assessing neurotoxic effects of MA. Low NAA levels have been reported in individuals with various neurological diseases and psychiatric disorders, including traumatic brain injury (Ross et al., 1998), ischemic brain disease (Sappey-Marinier et al., 1992), Alzheimer's disease (Heun et al., 1997), multiple sclerosis (Landtblom et al., 1996), schizophrenia (Yurgelun-Todd et al., 1996) and substance use disorders such as alcohol (Schweinsburg et al., 2001) and heroin abuse (Haselhorst et al., 2002). Prior MRS studies in abstinent MA users have also reported abnormal metabolites levels of NAA, creatine (Cr), choline-containing compounds (CHO) and *myo*-inositol (MI) in frontal lobes and the basal ganglia (Chang et al., 2005; Ernst et al., 2000; Nordahl et al., 2002, 2005; Sekine et al., 2002).

It has been reported that abstinent MA users have lower NAA levels in the anterior cingulate (Nordahl et al., 2002, 2005) but not in the frontal white matter (Nordahl et al., 2002). Furthermore, MA users who recently initiated abstinence had a high CHO/NAA ratio in the anterior cingulate region whereas those who initiated abstinence more than 1 year ago did not (Nordahl et al., 2005). A trend for lower NAA levels in the frontal white matter of abstinent MA users has been reported by Ernst et al. (2000). There was an inverse correlation between NAA level and the total amount of MA usage. Recently, Chang et al. (2005) have reported that chronic MA abusers who tested negative for immunodeficiency virus (HIV) had decreased NAA concentrations in the frontal white and gray matter. However, the characteristics of MA-induced brain changes in humans, especially the relationship of toxicity to MA dose and recovery with abstinence, remain to be further studied.

There have been a number of reports regarding the recovery of MA toxicity with abstinence (Hwang et al., 2006; Kim et al., 2006; Volkow et al., 2001; Wang et al., 2004; Nordahl et al., 2005). Long-term abstinent MA-dependent subjects had greater regional cerebral perfusion and gray matter densities in specific brain regions compared to short-term abstinent subjects (Hwang et al., 2006; Kim et al., 2006). In addition, a recovery of dopamine transporter levels in striatum (Volkow et al., 2001) and the recovery of glucose metabolism in thalamus have been reported in longitudinal follow-up studies (Wang et al., 2004). Although Ernst et al. (2000) have shown an inverse relationship between the MA dose and NAA concentrations of white matter (Ernst et al., 2000), the relationship between clinical MA dose/abstinence and toxicity effects have not been widely reported in humans.

Based on the prior reports (Ernst et al., 2000; Nordahl et al., 2002), we hypothesized that lower absolute NAA concentrations would be found in gray and white matter of MA abusers, especially those who had been exposed to larger cumulative MA doses or who had been abstinent for only a short period of time relative to healthy comparison subjects. We also hypothesized that these NAA concentrations would negatively correlate with the severity of MA abuse, as indicated by the cumulative MA dose or the duration of abstinence.

In order to assess this, we performed a proton MRS study using high-strength 3 T MR scanner and measured the absolute concentrations of *in vivo* NAA, Cr, CHO and MI in the frontal gray and white matter of abstinent MA abusers and healthy comparison subjects. We also investigated the relationship between metabolite concentrations and clinical characteristics including the duration of abstinence and cumulative MA dose.

2. Methods

2.1. Subjects

Inclusion criteria were (1) ages: 19–49 years, (2) lifetime diagnosis of DSM-IV methamphetamine dependence, as determined by Structured Clinical Interview for DSM-IV (SCID-IV), (3) abstinence period longer than 4 weeks, and (4) cumulative intravenous MA use over 50.0 g. Exclusion criteria were (1) any current or past significant medical or neurological illness, (2) lifetime diagnosis of schizophrenia, bipolar disorder and other psychotic disorders, or any current axis I psychiatric disorders, as identified by SCID-IV, (3) antisocial 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 MR scanning.

Thirty MA abusers and twenty healthy comparison subjects were recruited through advertisements at local newspapers in Seoul, South Korea. The study protocol was approved by the Institutional Review Boards at Seoul National University Hospital and McLean Hospital. After a complete description of the study to the subjects, written informed consent was obtained. Participants have received the equivalent of approximately US$ 150 for participating in the screening and MR scanning procedures. To detect current substance use, urine screening was conducted in both groups at recruitment and at MR scanning. Information regarding lifetime exposure to drugs was obtained using the Addiction Severity Index (ASI) and interview.

Since the partial recovery of thalamic glucose metabolism has been reported in MA abuser with protracted abstinence (≥12 months), relative to short abstinence (<6 months) (Wang et al., 2004), MA abuser group has been divided into short-term (<6 months abstinence) and long-term (≥6 months abstinence). In our recently completed studies, the same basis for abstinence has been used (Kim et al., 2005, 2006). They were also divided into abusers with small (=<100 g) and large (>100 g) total cumulative MA dose lifetime exposure. Based on the descriptive statistics of over 10,000 MA abusers, the Korean Association Against Drug Abuse (KAAD) have reported that heavy users usually exceed the 100 g (approximately 2000 shots) within several years while light users do not cross this amount even after lifetime use.

2.2. Imaging acquisition

2.2.1. Magnetic resonance imaging (MRI). Brain MRI was performed using a 3.0 T GE whole body imaging system (GE VH/i, USA). A three-dimensional spoiled gradient echo pulse sequence was used to produce 248 contiguous sagittal images of 0.7-mm-thick (echo time (TE) = 14 ms, repetition time (TR) = 5.7 ms, inversion time (TI) = 400 ms, 256 × 256 matrix; field of view