Eur Arch Psychiatry Clin Neurosci (2001) 251 : 114–116

ORIGINAL PAPER

Thomas Obergriesser · Gabriele Ende · Dieter F. Braus · Fritz A. Henn

Hippocampal ^{1}H-MRSI in ecstasy users

Received: 24 July 2000 / Accepted: 27 April 2001

Abstract In recent years the illicit drug ecstasy (MDMA, 3,4-methylenedioxymethamphetamine) has come into widespread use among young people. Despite clear evidence for the neurotoxic potential of MDMA in animals, corresponding evidence in humans is limited to indirect findings. In an exploratory study we compared the hippocampal ^{1}H-MRSI (magnetic resonance spectroscopic imaging) spectra of five MDMA users with those of controls with no history of substance abuse. Although ^{1}H-MRSI is sensitive in detecting alterations in neuronal viability in association with diseases leading to neuronal degeneration, we were not able to demonstrate any differences in hippocampal ^{1}H-MRSI between MDMA users and controls.

Key words 3,4-methylenedioxymethamphetamine · Hippocampus · Nuclear magnetic resonance

Introduction

In recent years the illicit drug ecstasy (3,4-methylenedioxymethamphetamine, MDMA) has come into widespread use among young people. There is good evidence for a neurotoxic potential of MDMA in animals (Ricaurte et al. 1992). The available data suggest a distal alteration of central serotonergic neurons (McCann et al. 1998). Investigations in humans show indirect evidence of neurotoxic effects, such as memory impairment and altered EEG power (Bolla et al. 1998, Dafters et al. 1999). Reduced prolactin and cortisol responses to the serotonergic agonist d-fenfluramine further indicate long-lasting serotonergic system impairment after discontinuation of MDMA (Gerra et al. 2000). With positron emission tomography using the selective serotonin transporter radioligand carbon–11-labelled McN–5652, abstinent MDMA users showed decreased global and regional brain serotonin transporter binding compared to controls (McCann et al. 1998).

Magnetic resonance spectroscopic imaging (MRSI) provides a non-invasive method for the quantitative analysis of certain tissue compounds. Although ^{1}H-MRSI usually only allows the detection of NAA (N-acetylaspartate), creatine and choline signals, the advantages of a non-invasive method for in vivo studies are obvious. In temporal lobe epilepsy MRSI signal differences can be used to determine the affected hemisphere (King and Baltuch 1998). In schizophrenic patients decreased hippocampal NAA signals may reflect the neuronal dysfunction associated with this disease (Deicken et al. 1998).

As MDMA has been shown to be associated with serotonergic axonal degeneration in animals (Ricaurte et al. 1992), we opted to focus on the hippocampus as a region of high serotonergic synapse density. We hypothesized that impaired neuronal viability associated with MDMA consumption would reflect in a decrease of NAA signals.

Purpose

The purpose of this study was to explore whether ^{1}H-MRSI could serve as a means for investigating the effects of MDMA use on the hippocampus. In preparation of future longitudinal studies on the temporal aspects of changes associated with MDMA use, our second goal was to test the temporal reliability of our MRSI measurements.

Materials and Methods

Using MRSI we studied 5 ecstasy users (age 25.7 ± 2.7 years) and 5 age-matched healthy controls (age 26.6 ± 2.9 years) with no history of

T. Obergriesser (✉) · G. Ende · D. F. Braus · F. A. Henn
NMR-Research
Central Institute of Mental Health
P. O. Box 12 21 20
68072 Mannheim, Germany
E-Mail: Tom@skullslicer.zi-mannheim.de

EAPCN 320

substance abuse. MRSI studies of healthy controls were carried out twice with an interval of 3 to 7 days. Ecstasy users had consumed at least 100 doses (range 120–350 doses) of MDMA each for three to six years without showing significant psychiatric alterations based on the patient's history, the positive and negative syndrome scale (PANSS), and the Beck depression inventory (BDI). Ecstasy users and controls did not differ in the Wisconsin Card Sorting Test (WCST) or in the subtest working memory of the "Testbatterie zur Aufmerksamkeitsprüfung" (TAP). All ecstasy users were drug free at the time of examination according to their own report. The last ingestion of MDMA had taken place between three weeks and four months prior to testing.

All ^{1}H-MRSI studies were performed on a 1.5 T Siemens Vision MRI/MRS system equipped with a standard head coil. For MRSI localization 2D FLASH images in coronal, sagittal and oblique transverse orientation were acquired. Oblique transverse images were angulated parallel to the long axis of the hippocampus.

A PRESS MRSI technique with TE = 135 ms and TR = 1800 ms was applied. PRESS volume pre-selection was performed parallel to the transverse images and included both hippocampi. A MRSI field of view (FOV) of 210 × 210 mm and a PRESS volume thickness of 15 mm was used with circular k-space sampling equivalent to a maximum of 24 × 24 phase encoding steps. Postprocessing including Gaussian line fitting for NAA, creatine (Cr) and choline (Ch) was carried out using an automated fit algorithm (Soher et al. 1998, Young et al. 1998 a, Young et al. 1998 b). A k-space apodization resulting in an effective voxel size of approximately 4 cc and zero filling to 32 × 32 k-space points was applied prior to the spatial Fourier transformation. Zero-filling from 512 to 1024 time domain data points and Gaussian multiplication corresponding to 0.6 Hz line broadening were carried out prior to the time domain Fourier transformation. The person conducting the interactive procedures was blind as to the user or non-user status of the test persons. For direct inter-subject comparisons of metabolite signals, metabolite signals were also corrected for coil loading. A more detailed description of the MRSI protocol and data processing is given in Ende et al. (2000).

For statistical comparisons MRSI data were subdivided into two groups, i. e., ecstasy users and controls. Two-tailed t-tests were used to determine differences in NAA, creatine and choline values as well as NAA/(Cr+Ch) ratios. Additionally, the findings in our control group were used to provide test-retest comparisons.

Results

The repeated MRSI measures in our controls showed the intra-subject variability of the NAA signals to be within 1 % to 5.8 % with a mean of 3.28 %. The individual differences for NAA/(Cr+Ch) ratios were 0.6 % to 6.5 % with a mean of 2.9 %.

The mean group results for NAA, Cr, Ch and NAA/(Cr+Ch) ratios have been summarized in Table 1. Although Ch signals showed a trend towards higher values in ecstasy users, none of the results reached statistically significant levels.

Table 1 Mean group results for NAA, Cr, Ch and NAA/(Cr+Ch) ratios in institutional units

Mean values ± SD [i. u.]	Ecstasy user (n = 5)	Controls (n = 5)
NAA	14.18 ± 1.77	14.35 ± 1.37
Creatine	8.10 ± 0.89	8.14 ± 1.1
Choline	9.73 ± 0.89	9.08 ± 1.2
NAA/(Cr+Ch)	0.80 ± 0.10	0.84 ± 0.07

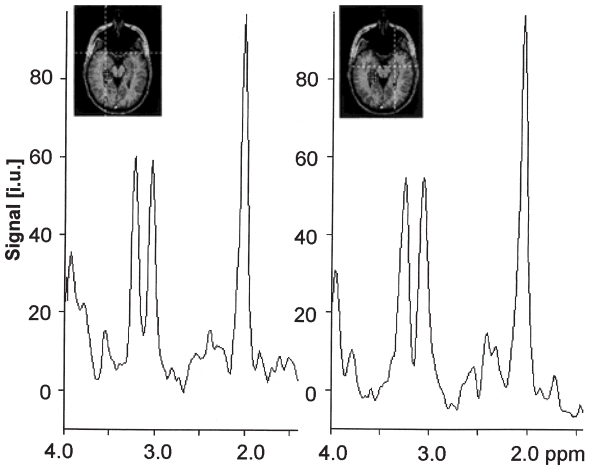

Fig. 1 Spectra from a repeated MRSI experiment in a healthy control showing the peaks assigned to NAA at 2.0 ppm, Cr at 3.0 ppm and Cho at 3.2 ppm. The location of the evaluated voxels is shown in the inset.

Discussion

Our exploratory ^{1}H-MRSI follow-up study showed no differences in hippocampal NAA or choline compounds between asymptomatic, abstinent MDMA users and controls.

The retest reliability of our MRSI study proved to be well within the reproducibility range determined for a single voxel STEAM technique (Choi and Frahm 1999) as well as for a single voxel PRESS technique (Hoshino et al. 1999). Thus, MRSI is well-suited for studies requiring test-retest reliability.

This lack of significant signal differences in NAA is consistent with recent findings of Chang et al. (1999 a) in a single voxel study of ecstasy users, who had examined the mid-frontal, mid-occipital, and parietal brain regions with short echo time (TE) single voxel MRS. Supporting our findings, they also found no changes for NAA, Cr and Ch but an increase in myo-inositol in the parietal white matter in ecstasy users. Since we used a PRESS MRSI technique with long TE, myo-inositol values could not be evaluated in our study.

A decrease in NAA signals is a quite sensitive marker for neuronal loss (Ende et al. 1997). This could already be demonstrated for abstinent crack cocaine users by Chang et al. (1999 b). Besides decreased NAA signals, the crack cocaine users examined showed an increase in myo-inositol signals. These signal alterations have been explained by neuronal loss and glial activation due to crack cocaine use.

Based on our data, MDMA seems not to lead to a decrease in hippocampal NAA signals as a sign for a profound disturbance of neuronal viability in distal serotonergic neurons. This view is supported by findings in squirrel monkeys where abnormal innervation patterns in MDMA-treated monkeys are not the consequence of loss of a particular serotonergic nerve cell group (Hatzidimitriou et al. 1999).

Due to our study design with all examined persons drug abstinent at the time of MRSI acquisition and with varying time intervals to the last ecstasy use we cannot exclude that there is a transient disturbance of neuronal viability. Furthermore, our study is limited to asymptomatic users. Therefore, MDMA may cause long-lasting neuronal alterations in more vulnerable brains with the consequence of neuropsychological deficits or psychopathology in the context of MDMA use. MRSI in combination with thorough neuropsychological testing seems to be a suitable approach to identify and characterize possible risk populations and to examine long-term effects on neuronal viability and function. Therefore, longitudinal MRSI studies including subjects with psychiatric alterations attributable to MDMA are needed.

References

Bolla KI, McCann DU, Ricaurte GA (1998) Memory impairment in abstinent MDMA ("Ecstasy") users. Neurology 51: 1532–1537

Chang L, Ernst T, Grob CS, Poland RE (1999 a) Cerebral (1)H MRS alterations in recreational 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users. J Magn Reson Imag 10: 521–526

Chang L, Ernst T, Strickland T, Mehringer CM (1999 b) Gender effects on persistent cerebral metabolite changes in the frontal lobes of abstinent cocaine users. Am J Psychiatry 156: 716–722

Choi CG, Frahm J (1999) Localized proton MRS of the human hippocampus: metabolite concentrations and relaxation times. Magn Reson Med 41: 204–207

Dafters RI, Duffy F, O'Donnell PJ, Bouquet C (1999) Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence. Psychopharmacology 145: 82–90

Deicken RF, Zhou L, Schuff N, Fein G, Weiner MW (1998) Hippocampal neuronal dysfunction in schizophrenia as measured by proton magnetic resonance spectroscopy. Biol Psychiatry 43: 483–488

Ende G, Laxer KD, Knowlton R, Schuff N, Matson GB, Weiner MW (1997) Temporal lobe epilepsy: bilateral hippocampal metabolite changes revealed at proton MR spectroscopic imaging. Radiology 202: 809–818

Ende G, Braus DF, Walter S, Weber-Fahr W, Henn FA (2000) The hippocampus in patients treated with electroconvulsive therapy. A proton magnetic resonance spectroscopic imaging study. Arch Gen Psychiatry 57: 937–943

Gerra G, Zaimovic A, Ferri M, Zambelli U, Timpano M, Neri E, Marzocchi GF, Delsignore R, Brambilla F (2000) Long-Lasting Effects of (±)3,4-Methylenedioxymethamphetamine (Ecstasy) on Serotonin System Function in Humans. Biol Psychiatry 47: 127–136

Hatzidimitriou G, McCann DU, Ricaurte GA (1999) Altered serotonin innervation patterns in the forebrain of monkeys treated with (±)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. J Neurosci 19:5096–5107

Hoshino Y, Yoshikawa K, Inoue Y, Asai S, Nakamura T, Ogino T, Umeda M, Iwamoto A (1999) Reproducibility of short echo time proton magnetic resonance spectroscopy using point-resolved spatially localized spectroscopy sequence in normal human brains. Radiation Medicine 17: 115–120

King D, Baltuch GH (1998) Magnetic resonance imaging and temporal lobe epilepsy. Acta Neurol Scand 98: 217–235

McCann DU, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA (1998) Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. Lancet 352: 1433–1437

Ricaurte GA, Martello AL, Katz JL, Martello MB (1992) Lasting effects of (±)3,4-methylenedioxymethamphetamine on central serotonergic neurons in non-human primates: Neurochemical observations. J Pharmacol Exp Therap 261: 616–622

Soher BJ, Young K, Govindaraju V, Maudsley AA (1998) Automated spectral analysis III: application to in vivo proton MR spectroscopy and spectroscopic imaging. Magn Reson Med 40: 822–831

Young K, Govindaraju V, Soher BJ, Maudsley AA (1998 a) Automated Spectral analysis I: formation of a priori information by spectral simulation. Magn Reson Med 40: 812–815

Young K, Soher BJ, Maudsley AA (1998 b) Automated spectral analysis II: application of wavelet shrinkage for characterization of non-parameterized signals. Magn Reson Med 40: 816–821