Metabolite Abnormalities in Rhesus Monkeys during Withdrawal of Methamphetamine: A ^{1}H MR Spectroscopy Study at 3T

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Introduction

Methamphetamine (METH), a powerful psychostimulant drug, can cause long-term alterations in dopaminergic, serotonergic, and glutamatergic systems. Human neuroimaging studies have demonstrated abnormalities in brain structure, function, and neurochemistry due to chronic METH use. However, human studies are often confounded by factors such as presence of pre-existing conditions (e.g., mental illness), differences in drug use patterns (regular or infrequent), and poly-drug use. In contrast, these confounding factors can be carefully controlled in animal models. Non-human primates provide valuable models of drug addition due to their similarity to humans in brain anatomy and function, physiology, and cognitive behaviors. Therefore, findings from non-human primate models can be more directly translated to humans. So far, there are very limited studies showing the metabolite changes in the abstinence of METH in humans and limited findings in non-human primates. In this study, we investigate metabolite levels in the brain of Rhesus monkeys during METH withdrawal using proton magnetic resonance spectroscopy (^{1}H-MRS).

Materials and Methods

Ten Rhesus monkeys (9 male and 1 female, 8-13 kg body weight), with a long history of methamphetamine exposure (8-10 years) and an average daily METH intake from 0.4 to 1.2 mg/kg, and 5 naive Rhesus monkeys (males) matching the age of METH-self-administered monkeys were used for the study. In the preparation for the MRI/MRS scan, anesthesia was induced by ketamine (10 mg/kg, im), transitioned to intravenous propofol (30-50 mg/kg/h) for intubation and transport to the MR Facility where it was discontinued and replaced by isoflurane. During the MRS scan, the anesthesia was maintained using 1.8-2.5% isoflurane in O_2. Vital signs (heart and respiration rates, end tidal CO_2, blood oxygen saturation, systolic and diastolic blood pressure) were monitored continuously. For the METH-abstinence group, the MRS scans were performed longitudinally in 5 separate sessions (1-day, 1-week, 1-month, 3-month, and 6-month abstinence, respectively). In each session, ^{1}H-MRS spectra were acquired from a single-voxel in the frontal lobe encompassing the dorsal anterior cingulate cortex (dACC) and from a single-voxel in the basal ganglia encompassing the striatum. Both regions have been implicated in METH addiction.

The MRI and ^{1}H-MRS scans were performed on a Siemens Allegra 3T scanner (Erlangen, Germany) using a NOVA birdcage coil for transmitting and two pieces of surface coils for receiving. Single-voxel PRESS spectral data were acquired from the frontal-lobe voxel ($18\times12\times10$ mm^3) that encompassed the dACC and from the basal ganglia voxel ($10\times11\times10$ mm^3) encompassing the striatum, based on the high-resolution T_2-weighted localizer images (see Fig. 1). The PRESS sequence parameters were TR/TE = 2000/30 ms, bandwidth = 2 kHz, sampling points = 2048, repetition = 600, 16-step phase cycling, total time = 20 min. Unsuppressed water signal was acquired with 4 TRs immediately following the ^{1}H-MRS scan. To secure better shimming, manual shimming was performed following the Siemens automatic shimming procedure. In order to correct for the CSF in each voxel for absolute spectral quantification, a whole-brain volume of high-resolution anatomical images was acquired using a 3D magnetization prepared rapid gradient echo (MPRAGE) T_1-weighted sequence on each session. Image segmentation was performed to obtain the CSF, gray matter, and white matter of the brain volume, using SPM with a recently published Rhesus monkey template [1]. Each voxel was then registered into the segmented brain volume to calculate the percentage of CSF in the voxel.

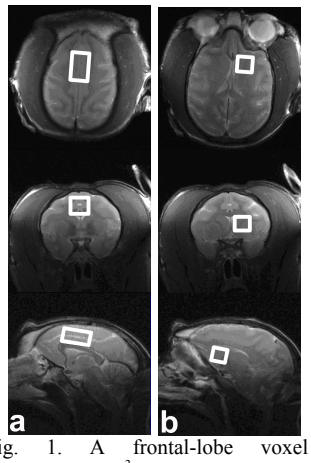

Fig. 1. A frontal-lobe voxel ($18\times12\times10$ mm^3) that encompassed the dACC (a) and a basal ganglia voxel ($10\times11\times10$mm^3) encompassing the striatum (b), on the high-resolution T_2-weighted localizer images.

The spectral data received from individual surface coils were combined by a complex weighting function obtained from a singular value decomposition (SVD)-based weighting estimation method [2]. After combination, spectral quantification was carried out with LCModel [3] using unsuppressed water signal for scaling and eddy current correction. The basis set consisted of the model spectra of alanine (Ala), aspartate (Asp), creatine (Cre), γ-aminobutyric acid (GABA), glucose (Glc), glutamine (Gln), glutamate (Glu), glycerophosphocholine (GPC), phosphocholine (PCh), lactate (Lac), *myo*-Inositol (mI), *N*-acetylaspartate (NAA), *N*-Acetylaspartylglutamate (NAAG), and taurine (Tau). Only the concentrations with a Cramer-Rao Lower Bound (CRLB) less than 20% were included into the final data analysis.

Results and Discussion

Fig. 2 shows two representative spectra from the frontal-lobe voxel that encompassed the dACC (a) and the basal ganglia voxel that encompassed the striatum (b) of the same monkey. The spectra from the frontal-lobe voxel generally demonstrated a better signal-to-noise ratio due to a larger voxel size and closer position to the surface coils. The linewidth of unsuppressed water peak mainly ranged from 17 to 30 Hz. The following metabolites had the CRLB of less than 20% for all the scans, Cre, Glu, tCho (GPC+PCh+Cho), mI, NAA, NAANAAG (NAA+NAAG), and Glx (Glu+Gln), with generally 3-4% for NAA, NAANAAG, and Cr+PCr, 4-5% for tCho and mI, 8-9% for Glu and Glx, and 11-20% for most Gln with some over 20%.

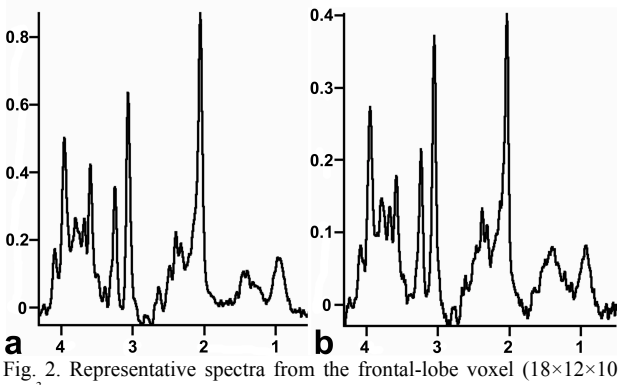

Fig. 2. Representative spectra from the frontal-lobe voxel ($18\times12\times10$ mm^3) that encompassed the dACC (a) and the basal ganglia voxel ($10\times11\times10$mm^3) that encompassed the striatum (b) of the same monkey.

There were no significant metabolite differences in the frontal lobe between the METH and control groups. However, animals with long-term METH exposure showed elevated tCho levels in the basal ganglia at early time points of abstinence (up to one month) and even after 3 months of drug withdrawal (1.33 at early abstinence and 1.37 after 3 months of METH withdrawal in the METH group and 1.06 in the control group, $p<0.03$ and $p<0.02$, respectively). In addition, tCho/NAANAAG in the basal ganglia was also significantly higher in both the early abstinence (0.20) ($p < 0.03$) and long abstinence (0.20) ($p < 0.05$), compared with the control group (0.15). In contrast, the Cre level in the striatum was significantly lower in early abstinence (7.30) ($p <0.02$), compared to the control group (7.88). There were no differences between the METH and control groups observed after 3 month of drug withdrawal. The data on elevated tCho level are consistent with the findings in human METH users in abstinence and suggest prolonged effects of METH after withdrawal [4].

References

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