Preliminary studies of MDMA induced brain hyperthermia using spectroscopic imaging and 1H-[13C]MRS

L. Jiang[1], R. A. de Graaf[2], and K. L. Behar[3]

[1]Diagnostic Radiology, Magnetic Resonance Research Center, Yale University, New Haven, CT, United States, [2]Diagnostic Radiology, Magnetic Resonance Research Center, Yale University, [3]Psychiatry, Magnetic Resonance Research Center, Yale University

Introduction

3,4-Methylenedioxymethamphetamine (MDMA) is a heavily abused psychostimulant. A major life threatening effect of MDMA and structurally similar analogs is the induction of hyperthermia. Although MDMA-induced hyperthermia is well characterized in peripheral tissues, the mechanism and cellular location of thermogenesis in brain has not been identified. In this study, we report on the feasibility of combining brain temperature mapping using the temperature-dependent frequency shift of water relative to NAA (1,2) with ^{1}H-[^{13}C] MRS measurements of ^{13}C turnover following acute MDMA-induced hyperthermia.

Materials and Methods

Experiments were conducted at 9.4 T (magnet) using Sprague-Dawley rats (230±20g), fasted overnight, and anesthesized with urethane, tracheotomized and ventilated (30% O_2, 70% N_2O). A femoral artery and vein were cannulated for monitoring of blood pressure, blood gases, and infusion of bicarbonate as needed, respectively. MDMA was administered by intraperitoneal catheter. Ambient bore temperature was maintained at 24°C and core temperature (before MDMA injection) by a heating pad using a circulating water bath. Magnetic field homogeneity was optimized by FASTMAP (3). Spectroscopic imaging (SI) was conducted over a 2x2 cm FOV with a matrix size of 20x20 (circular k-space sampling), an interscan interval of 2s, and TE of 100 ms, which was sufficient to reduce but not eliminate the water resonance, allowing NAA and water to be acquired in the same voxel simultaneously. Brain temperature was calculated for each voxel by measuring the frequency separation of water and NAA (1,2) or creatine. The ^{1}H-[^{13}C] MRS measurement was acquired in a single volume of cortex (6x5 x6 mm^3) using the fully adiabatic LASER sequence (4). [1,6-^{13}C]Glucose was infused intravenously after brain and body temperature had reached a stable plateau after MDMA injection (30-45 mg/kg, i.p.), which was after 1h for the doses used. ^{13}C labeled amino acids were quantified using a in-house version of LCmodel (5,6). Calibration experiments were conducted using a solution of NAA and creatine in phosphate buffer (pH 7.4) over a temperature range of 25 to 50 °C.

Results and Discussion

Calibration studies conducted in vitro and verified in vivo gave a sensitivity for this method of 4.43 Hz/°C, allowing temperature changes to be measured in the brain in vivo with an accuracy of ~0.2 °C based on spectral resolution. After a single dose of MDMA, body temperature increased from 36.6 ± 0.5°C to 39 ± 1°C within ~100 minutes. The temperature map derived from spectroscopic images showed regional differences in temperature elevation, with lower temperatures recorded in the cortex and higher values in the hippocampus. The higher hippocampal temperatures may reflect lower blood flow and heat dissipation, increased oxidative metabolism, or possibly both. The plateau in brain temperature after acute MDMA treatment provided a quasi thermal steady-state of sufficient duration to permit the measurement of ^{13}C metabolite turnover during an infusion of [1,6-^{13}C]glucose (Fig. 1D). Preliminary results suggest that glutamate and glutamine ^{13}C labeling is increased during MDMA hyperthermia, suggesting a rise in heat-generating oxidative metabolism and demonstrating the feasibility of assessing metabolic fluxes under hyperthermic conditions in vivo.

Conclusion

SI brain temperature mapping revealed regional differences in temperature after acute MDMA treatment, with higher values recorded in hippocampus than cortex. Regional measurements of temperature, oxidative metabolism (from ^{13}C turnover), and blood flow after MDMA and other methamphetamine derivatives may provide new insights into the mechanism of thermogenesis and brain temperature regulation in vivo.

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References

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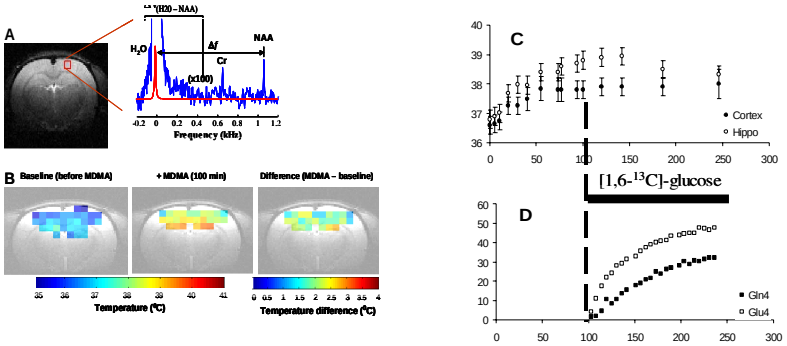

Fig. 1. A) Illustration of spectroscopic imaging, and temperature map derived from the temperature dependent chemical shift of water relative to NAA, and creatine. B) SI temperature maps of a coronal section of rat brain measured before MDMA injection (baseline, leftmost), 100 min after injection of MDMA (40 mg/kg, i.p.) (middle), and for their difference (MDMA minus baseline, rightmost). C) Time course of MDMA-induced temperature changes in cortex and hippocampus. D) [4-^{13}C] glutamate (Glu) and [4-^{13}C] glutamine (Gln) time courses for a rat administered [1,6-^{13}C]glucose in the period of stable hyperthermia between 100-240 min after MDMA injection.