Distribution of temperature changes and dynamics in rat brain after 3,4-methylenedioxymethamphetamine (MDMA) injection by ^{1}H CSI

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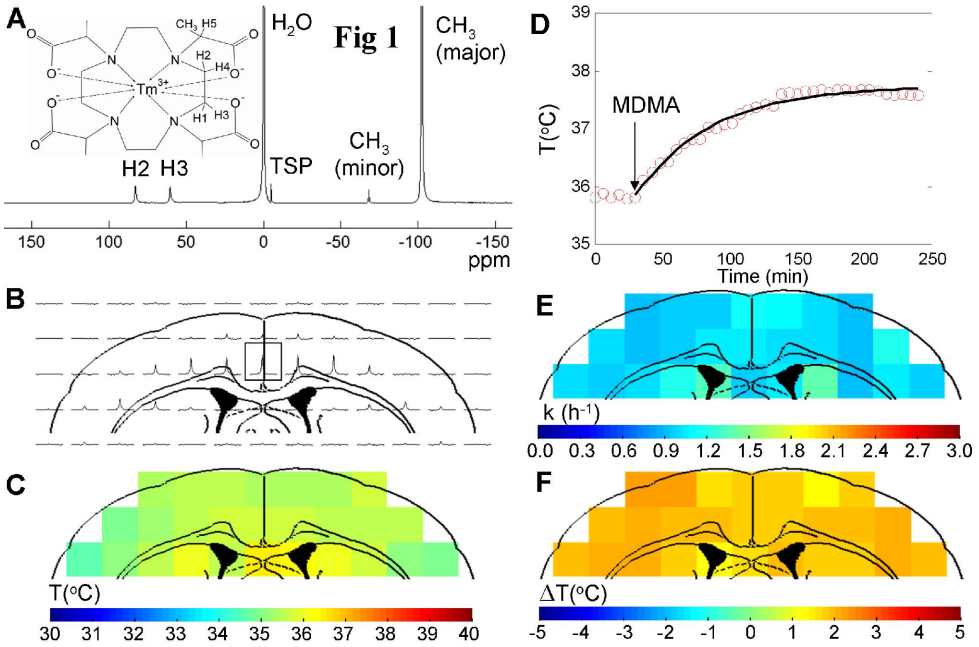
INTRODUCTION (+/-) 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) is a heavily abused psychostimulant which has seen explosive growth in its use during the last decade, particularly among the young **[1]**. The main acute effects of MDMA toxicity are associated with serotoninergic and sympathomimetic activation (serotonin syndrome) **[2, 3]**, but effects on other neurotransmitters systems (dopamine, norepinephrine, acetylcholine) are involved as well. The most severe and potentially fatal acute effects of MDMA involve extreme hyperthermia and its consequences on multiple organ systems, e.g., rhabdomyolysis, coagulopathy, kidney, heart, and liver failure **[3, 4]**. MDMA-induced hyperthermia has been demonstrated in rat brain **[5]**, as well as peripheral tissues, and shown to be greatly enhanced by stressful environmental conditions (e.g., social stress, high ambient temperatures, etc.). In animals MDMA mainly depletes and damages fine terminals and axons of serotoninergic neurons, but release of other monoamines, e.g., dopamine and norepinephrine, are now well documented **[4, 6]**. The magnitude, distribution, and dynamics of MDMA induced temperature changes are thus of critical importance in neurotoxicity, although measurements of brain temperature are rare in studies of MDMA's neurotoxicity where core body temperature is most frequently reported. New methods to image brain temperature could provide new insights into the role of hyperthermia in the toxicity of MDMA. Recently, we showed that temperature distributions in rat brain can be obtained within minutes by using a new temperature-sensitive probe which is based on the complex between the thulium ion (Tm^{3+}) and the macrocyclic chelate 1,4,7,10-tetraazacyclododecane-1,4,7,10- tetramethyl-1,4,7,10-tetraacetate or $DOTMA^{4-}$ **(Fig. 1A) [7]**. The methyl ^{1}H chemical shift of $TmDOTMA^-$ shows relatively high temperature sensitivity **[7]** and is pH-independent **[8]**. In the present study we use the $TmDOTMA^-$ agent to measure time-dependent temperature distributions and from these we calculate the maps of temperature changes and those of MDMA-induced warming rate constants in rat brain.

MATERIALS AND METHODS ***Animal preparation:*** Sprague-Dawley rats (250-300 g) were tracheotomized and artificially ventilated (30% O_2). The animals were anesthetized with an intraperitonial injection of urethane (1.3 g/Kg). A subcutaneous line was inserted for administration of MDMA (20 mg/kg) and an intravenous line for administration of D-tubocurarine chloride (1 mg/kg/hr) or $TmDOTMA^-$ (150-200 µmol/hr). An arterial line was used for monitoring physiology (blood pH, pO_2, pCO_2) throughout the experiment. The anesthetized rats were prepared with renal ligation as previously described **[7]**. Initially, $TmDOTMA^-$ was continuously infused for ~2 hours, followed by the MDMA injection. ***In vivo (n=3):*** All CSI data **(Fig. 1B)** were obtained on a modified 11.7 T Bruker horizontal-bore spectrometer (Billerica, MA) using a ^{1}H resonator/surface coil RF probe. A gaussian pulse of 200 µs was used for excitation of a 6 mm slice with FOV of 2.56 cm x 2.56 cm. The following parameters were used: 16x16 encode steps, TR=11 ms, 100 averages and 4 min 40s acquisition time. The spectra were line broadened (150 Hz), phased (zero order) and baseline corrected (first order) in a similar fashion in Matlab 5.3. The temperature maps **(Fig. 1C)** were calculated from the chemical shifts of $TmDOTMA^-$ methyl group according to the equation: $T=346+4.6\cdot\delta_{CH3}+0.0152\cdot\delta_{CH3}^2$ **[7]**. For each animal, the MDMA-induced warming rate constants were calculated by fitting the temperature variation over time to a single exponential function **(Fig. 1D).**

RESULTS AND DISCUSSION The results in **Fig 1** represent the results for one animal. The results show that the $TmDOTMA^-$ signal is localized mainly in the cortical regions due to limited excitation/detection of the surface coil. Although the signal is lower in the subcortical regions of the brain, the corresponding SNR values are still large enough to allow temperature determination with good accuracy **(Fig. 1B)**. In this experiment, the average brain temperature before MDMA injection was 35.6 ± 0.4 ^{0}C **(Fig. 1C)** and increased to 37.7 ± 0.4 ^{0}C (data not shown) after 3 hours from the injection. The calculated temperature variation for the central voxel, boxed in **Fig. 1B,** is shown in **Fig. 1D.** The distribution of the MDMA-induced warming rate constants is shown in **Fig. 1E.** The results indicate a relatively homogenous distribution of warming rate constants, with subcortical regions showing slightly faster temperature increase than the cortical regions. The average rate constant of MDMA-induced temperature change was 1.05 ± 0.13 h^{-1}, while the average temperature change was 2.1 ± 0.3 ^{0}C. Although the distributions of both warming rate constants and temperature changes are relatively homogenous within the same animal **(Fig. 1E and Fig.1F)**, somewhat larger variations are observed when comparing different animals**.** The average warming rate constant (for all the animals investigated) was 1.4 ± 0.4 h^{-1}, while the average temperature change was +1.7 ± 0.4 ^{0}C. On average, the brain temperature increased from 35.5 ± 0.2 ^{0}C to 37.2 ± 0.5 ^{0}C, while the core temperature increased from 37.4 ± 0.4 ^{0}C to 39.8 ± 0.4 ^{0}C. Similar results were reported in another study on MDMA-induced temperature changes in the rat brain, which showed slightly lower temperatures in the cortex than in the hippocampus region **[9]**. These results are also in good agreement with another rat study which showed that the temperature dynamics in both nucleus accumbens and hippocampus were very similar, with changes of about +1.4 ^{0}C for an MDMA dose of 9 mg/kg **[5]**. In summary, the current results indicate that the temperature increase in the rat brain after a dose of 20 mg/kg MDMA is relatively homogenous, with subcortical regions showing slightly faster temperature increase than the cortical regions.



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