Manganese-Enhanced MRI Non-Invasively Reveals the Degeneration of Fasciculus Retroflexus Induced by Meth-Amphetamine

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Synopsis

A psychostimulant, meth-amphetamine (MA), degenerates the sheath part of fasciculus retroflexus (FR) which is a neuronal pathway projecting from lateral habenula nucleus to ventral tegmental area and substantia nigra pars compacta. In the present study, manganese-enhanced MRI (MEMRI) was applied to investigate the chronic MA-induced neurotoxicity on FR tract. Our results show that FR tract can be visualized and the manganese-enhanced signal intensity of FR tract in MA-treated rat is lower than that of control rat. MEMRI is proved to be a promising method to evaluate the damages of neuronal connectivity in psychostimulant-dependent animal model.

Introduction

Meth-amphetamine (MA), a commonly-abused psychostimulant, affects the midbrain dopamine system which is involved in functions like motor ability, emotion and thought. The midbrain dopamine system is consisted of the dopaminergic neurons in ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), which project axons to nucleus accumbens (NAc), prefrontal cortex (PFC) and striatum. NAc, PFC and striatum subsequently innervate lateral habenula nucleus (LHN). LHN then sends negative feedback projection to VTA and SNc through the sheath part of fasciculus retroflexus (FR) tract [1]. The chronic exposure of MA causes brain dysfunction in MA-abuser [2], suggesting the damaged FR tract. Histological study showed that the repeated MA injections into rat selectively induced the degeneration of FR tract. However, conventional histological techniques for tract tracing rely on the sectioning of brain, which is time-consuming and excludes the long-term study on the same subjects. Therefore, *in vivo* methods need to be developed to evaluate the degenerating axons in FR for studying the role of FR tract in psychostimulant-dependent subjects. Recently, manganese (Mn^{2+})-enhanced MRI (MEMRI), a newly-developed MR technique, has been applied for the *in vivo* mapping of the neuronal pathways with the resolution comparable to histology [3]. In the present study, MEMRI was applied to non-invasively evaluate the degeneration of FR induced by MA.

Material and Method

Animals: MA was intraperitoneal injected into rats (Sprague-Dawley, male, 250-350 g) with does of 10 mg/kg once per day consecutively for five days. After MA treatment, two drug-free days were given and then stereotaxic injection of $MnCl_2$ (1.0 M, 0.015 μl) into LHN [AP: -2.8 mm, ML: 0.6 mm, DV: 4.6 mm] was performed on four MA-treated rats and three control rats.

MRI: All MRI scans were performed on a PharmaScan 70 / 16 7.0 T scanner (Bruker, Germany) before and 24 hr after $MnCl_2$ injection. Axial images were obtained in the same location (FOV = 2.56 cm, slice thickness = 1 mm, matrix = 256 * 128). T_2-weighted image (T2WI) was acquired with fast spin-echo sequence (TR = 4000 ms, effective TE = 70 ms, NEX = 8), and T_1-weighted image (T1WI) was obtained with spin-echo sequence (TR = 700 ms, TE = 10.3 ms, NEX = 8).

Data analysis: The signal-to-noise ratio (SNR) was calculated from T1WI. The SNR ratio was derived from the SNR of ipsilateral VTA / SNc divided by the SNR of contralateral VTA / SNc. All data analyses were performed by using MRVision (MRVision Co., Menlo Park, CA).

Results

As shown in fig. 1, 24 hr after $MnCl_2$ stereotaxic injection into LHN of normal rats, the FR tract and VTA / SNc innervated by FR were enhanced. In contrast to normal rats, the FR tract and VTA / SNc of chronic MA-treated rats were not significantly enhanced by Mn^{2+}, probably reflecting the decreased efficiency of axonal transport of damaged FR tract. In fig. 2, the quantified data showed that in control rats, the SNR of ipsilateral VTA / SNc was higher than that of contralateral side, indicating that Mn^{2+} was transported from LHN to VTA / SNc through FR tract. However, in rats treated with MA, the SNR of ipsilateral VTA / SNc was essentially the same with that of contralateral side, suggesting the degeneration of FR tract.

Discussion

The rat with damaged FR tract has been proposed as a model for addiction and drug-induced psychosis in human [1]. The FR tract is consisted of two components, the core part and the sheath part. Histological study showed that the chronic MA treatment selectively damages the axons in the sheath part of FR to VTA / SNc, but not the axons in the core part of FR to interpeduncular nucleus (IP) [1].Consisted with histology, the results show that in MA-treated rats, the decreased signal intensity was observed in VTA / SNc but not in IP, suggesting that Mn^{2+} is an excellent *in vivo* tract tracer to discriminate two close neuronal pathways. The present study demonstrates that MEMRI can be used as a valuable tool to study the role of FR in MA-induced brain dysfunction.

Reference

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[2] Paulus et al. (2002) Neuropsychopharmacology 26: 53-63.
[3] Saleem et al. (2002) Neuron 34: 685-700.

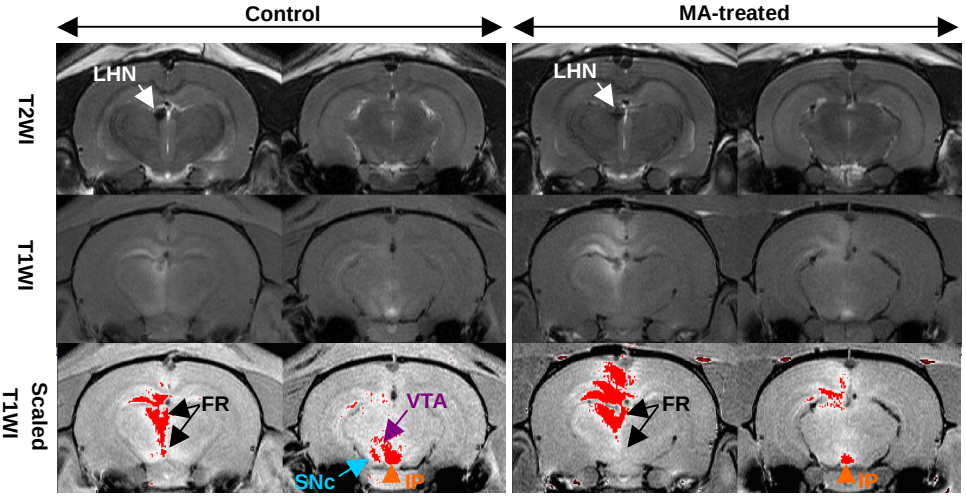

Fig. 1. MEMRI non-invasively revealed the degeneration of FR induced by chronic MA treatment. White arrow, LHN injected with Mn^{2+}; black arrows, FR; blue arrow, SNc; purple arrow, VTA; orange arrow head, IP.

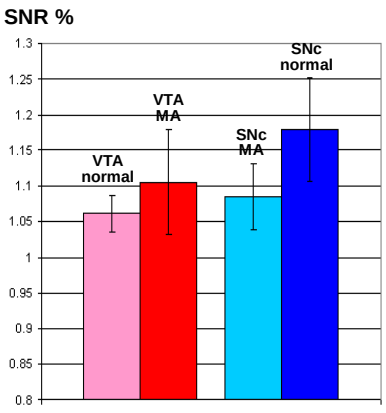

Fig. 2. The quantified Mn^{2+}-enhanced SNR ratio in VTA and SNc. From left to right, the ratio of VTA in MA-treated rat, the ratio of VTA in normal rat, the ratio of SNc in MA-treated rat, the ratio of SNc in normal rat.