Methoxamine Titration Induced BOLD Signals in Rat Brain: Implication on Pharmacological MRI Signal Induced by Cocaine

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Introduction. Pharmacological MRI (phMRI) methodologies have been used to localize cocaine's acute effects and detect changes in regional brain activity in humans (1). This provides a non-invasive way to investigate the human drug addiction mechanism for the first time. However, the changes in microvascular oxygenation that alter BOLD signals may be affected by cocaine at any number of levels: the neuron, blood vessel or, indirectly via changes in mean arterial blood pressure (MABP) as a result of cocaine's effects on the periphery. A cerebral vasoconstriction in the human brain during cocaine administration has been reported (2). As a confounding factor to CNS BOLD signals induced by a drug challenge, MABP perturbation has been investigated in a previous study (3) by employing cocaine methiodide (CM), reported to share similar cardiovascular effects of cocaine, however, cannot pass the blood-brain-barrier. We found that CM-induecd MABP increase only produces scattered BOLD signals inside the rat brain (3). Due to unknown effect of CM on vasculature, it is less clear whether increased cardiac output, increased peripheral resistance or a combination effect induced high MABP with little effect on BOLD signals in the rat brain. The stability of CM in the blood is yet unclear (4). Therefore, it is also questionable whether the observed scattered BOLD signals in the rat brain after CM administration came from cocaine's effects, which could be metabolized from CM. In order to determine the specific brain regions that are responsive to increased MABP due to cocaine's peripheral constriction effects, methoxamine (MX), a known α-receptor agonist acting on peripheral vascular with a relatively short half-life (several minutes) with no direct cerebral vascular effect (5) was employed to mimic the cocaine (5.0mg/kg) induced MABP profile by titration in the present study. It is hypothesized that cocaine and MX induced high MABP due to peripheral vascular constriction do not significantly affect the BOLD signals in the rat brain. A stable CBF under MABP perturbation will be tested in a separate bench study using Laser-Doppler Flowmetry (LDF). Cerebral autoregulation is proposed.

Materials and Methods. *Animal preparation:* Twelve male Sprague-Dawley rats, weighing 300-350g, were employed. The details of animal preparation for fMRI study were described in Ref.3. Briefly, seven rats were tracheotomized under urethane anesthesia (1.2 g/kg) and artificially ventilated. The right femoral vein and artery were cannulated for MX delivery by pump and monitoring MABP using Codas, respectively. *fMRI experiments:* fMRI experiments were performed on a Bruker Medspec 3T/60cm scanner using a custom-built, 2-inch long, 1.5-inch-diameter RF birdcage volume coil, inserted into an in-house-made cylindrical local gradient coil. A single-shot, gradient echo EPI sequence was used for functional imaging with FOV=3.5 cm, slice thickness=2 mm, image matrix=64 x 64, giving an in-plane image resolution of 550 x 550 µm, TR=1 sec, TE=27.2 ms, and bandwidth=±62.5 kHz. *LDF measurement*: CBF changes of five rats under increased MABP challenges (10 min) below 160 mmHg were evaluated by LDF in a separate bench study employed with similar fMRI settings with urethane anesthesia. LDF probes were positioned bilaterally over the somatosensory cortex. *Data analysis:* The BOLD fMRI signal in each voxel was fit with a non-linear beta model using AFNI software. Voxels were considered significantly activated based on an F test ≥ 10 (correspond $p<0.01$ for each voxel). Nine regions of interest (ROI) were defined from four coronal anatomical slices. The regions are: prefrontal cortex, cingulate cortex, nucleus accumbens, olfactory tubercle, caudate and putamen, parietal cortex, hypothalamus, thalamus and hippocampus. The BOLD response index was a multiplication of percentage of activated volume and their percentage change of signal intensity after drug or saline administration was determined for each ROI. ANOVA was employed to differentiate the BOLD signal induced by MX, cocaine, or CM.

Results. Cocaine-induced MABP increase profile can be mimicked by MX titration very well (Fig.1). MX induced significantly less BOLD response index (3) among all ROIs compared to cocaine at a dose of 5.0 mg/kg. No significant difference was found between MX and CM (7.5mg/kg) induced BOLD response index (Fig. 2, Table 1). The MABP increase (< 160 mmHg) did not change the measurement of CBF (Fig. 3).

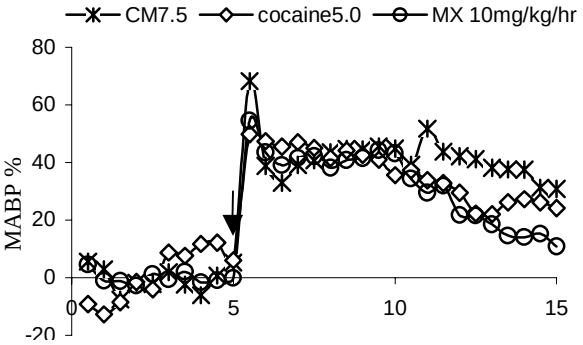

Fig. 1. Similar MABP profile among MX titration, cocaine and CM.

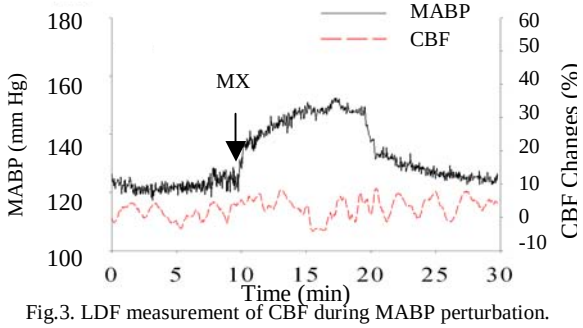

Fig.3. LDF measurement of CBF during MABP perturbation.

Table 1. BOLD response index comparison among MX, cocaine and CM.

	+ BOLD			- BOLD		
	MX	COC5.0	CM7.5	MX	COC5.0	CM7.5
Ave	0.5±1.47*	334±75	6±7	-1.6±1.96*	-1042±498	-69±61

*: $p<0.05$, comparison between MX and cocaine

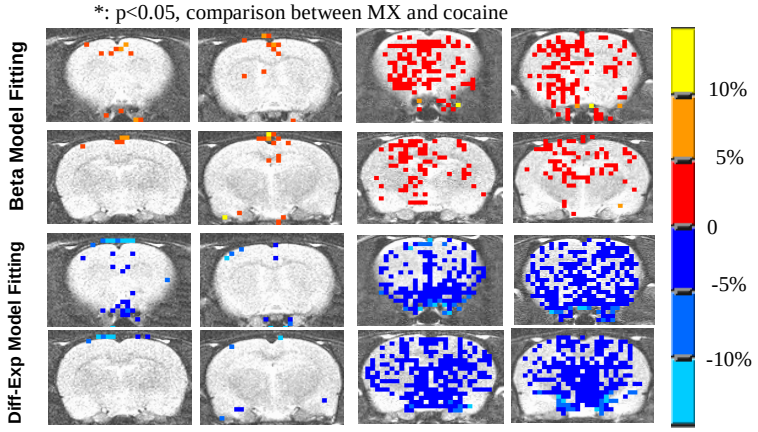

Fig.2. Drug-induced positive and negative BOLD signal changes overlaid on RARE.

Discussion. As demonstrated in Figs. 1-2 and Table 1, although MX mimics cocaine induced MABP profile, it did not induce significantly BOLD signals in the rat brain. It is clear that autoregulated CBF remains stable during MABP perturbation (Fig.3). By comparing MX-induced BOLD signal changes with cocaine-induced changes, we could extract information about cocaine-induced neuronal activity and the neuronal circuits responsible for cocaine-induced brain function.

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