Mechanisms of a Negative BOLD Response to Acute Cocaine Administration in Rat Brain

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INTRODUCTION Functional MRI methods have been increasingly used to investigate cocaine's effects on neural circuitry in humans and in animal models in recent years and the negative BOLD responses after systemic administration of cocaine have been reported [1-4]. Although previous studies suggested that the cocaine-induced negative BOLD responses could be an effect of neural-based vascular constriction or an increase in deoxyhemoglobin concentration in the large draining veins, the detailed mechanisms responsible for the negative BOLD response remain unclear. In the present study, we will employ high resolution fMRI method at a high magnetic strength to evaluate the relationship between the negative BOLD change and large vessel change.

METHODS **Animal preparation:** Eleven cocaine naïve male Sprague–Dawley rats (280g–330 g) were studied. The right femoral vein and artery were catheterized to administer cocaine and monitor physiologic parameters, respectively. Tracheotomy was performed and mechanical ventilation with a small animal ventilator was provided. Rats were anesthetized with 2.5% gaseous isoflurane during surgery and immobilized in an headset. All fMRI data were acquired under a continuous infusion of medetomidine (1 ml/h; 0.1 mg/kg/h) and pancuronium bromide (2mg/kg/h) through access of the tail vein. Intravenous saline or cocaine were administered 5 min into the 20 min long scan, using a 0.3-ml injection volume in 20s. Seven rats were given a cocaine dose of 5mg/kg and four rats were given 2.5mg/kg dose. **MRI methods:** All experiments were carried out on a Bruker AVANCE 9.4T/30-cm scanner with a custom-built surface receiver coil and a linear transmit coil. An initial RARE anatomical scan was acquired with a 256×256 matrix size, FOV=35mm, 15 slices, and 1 mm slice thickness. MR angiography (MRA) was performed with a 256×256 matrix size, FOV=30.7mm, 200 slices, and 0.4 mm slice thickness. All EPI parameters were as follows: 96×96 matrix size (zero-filled out to a 128×128 matrix size), TR=2000 ms, FOV=35mm, 15 slices, 1 mm slice thickness, and 600 time repetitions. **Data analysis:** Analysis of Functional NeuroImages (AFNI) software was employed to perform all fMRI analyses. Regions of interest (ROI) were defined based on the presence of the negative BOLD signal. The changes in vessel size were determined based on the presence of the negative BOLD signal before and after acute cocaine administration. A correlation analysis evaluated the relationship between the changes of the negative BOLD signal and the changes of the vessel size upon acute cocaine administration.

RESULTS A sharp negative BOLD signal (figure 1) was identified on cortical and subcortical surface around the large vessels about 20s to 30s after acute cocaine administration and lasted for about 40s to 50s. No negative BOLD signal was seen after saline administration. The average negative BOLD magnitude was 13.64±5.02% for a cocaine dose of 5mg/kg and 7.98±2.18% for 2.5mg/kg, respectively and were significantly different (p=0.012). Large vessel size increased 41.53±7.54% in the 5mg/kg group (figure 2) and 24.30±6.94% in the 2.5mg/kg group during the period of the negative BOLD signals, and was dose-dependent (p=0.007). Data from MRA experiments showed that the regions with negative BOLD signals were located at the large vessels (figure 3). A significant correlation between the negative BOLD change and the vessel size change was observed (n=11, p=0.0026, in figure 4). Interestingly, the mean arterial blood pressure (MABP) decreases about 20s to 30s after cocaine injection and remained in a decreased state for about 40s to 50s. The MABP decrease of 30.44±3.74% was observed for the 5mg/kg group and 9.74±4.00% for the 2.5mg/kg group, and the MABP decrease was dose-dependent (p=0.033). However, there was no significant correlation between the negative BOLD change and the MABP change (n=9, p=0.36).

DISCUSSION and CONCLUSION We observed significant negative BOLD signals, large vessel dilation in the rat brain and significant MABP decrease after cocaine administration during the transient period of the negative BOLD signal. Furthermore, a significant correlation existed between the changes in the negative BOLD and the changes in the vessel size. Previous studies suggested that acute cocaine administration may induce arterial vessel constriction and increase in MABP. In turn, the vessel constriction may result in decreased blood flow and decreased artery size due to the smooth muscle effect. These effects would induce a negative BOLD signal due to the increase in deoxyhemoglobin concentration. However, the present study showed transient increase in the vessel size and decrease in MABP after cocaine administration. To explain this apparent contradiction, it is suggested that the vessels with increased size may be due to the transient dilation of the arterioles surrounding the large vessels [5,6]. It is possible that when the arteries transiently respond to acute cocaine administration and dilate, this action surrounding the vein could change the vein size. The mechanically increased vessel size could result in the decreased BOLD signal because the brain tissue is replaced by the blood. This transient effect can be reversed after 40-50 seconds by the autoregulatory mechanism. In other words, this negative BOLD signal could be induced by vascular response instead of neural activity. In conclusion, our results suggested that the transient negative BOLD signals could result from cocaine-induced vessel dilation in the rat brain observed by using high-resolution fMRI study at high field strength.

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ACKNOWLEDGEMENTS This work was supported by NIH Grant EB 01820.

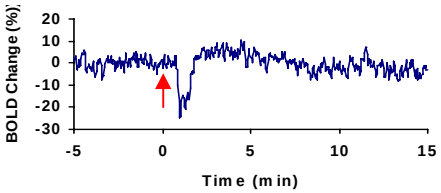

Fig. 1. Time courses after 5mg/kg cocaine administration in the rat brain (the red arrow indicated the time point of cocaine administrated) demonstrated a sharp negative BOLD signal 30s after cocaine injection and lasting for 40s

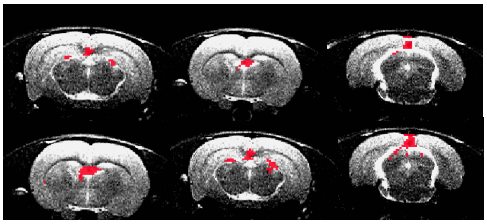

Fig. 2. Change of large vessel size before and during the period sharp negative BOLD signals appeared after cocaine administration. Pictures in top row showed large vessels (red) before cocaine administration. Pictures in the bottom row showed enlargement of the large vessels (red) after cocaine administration. The increase in vessel size (%) reversely correlates with the negative BOLD signal.

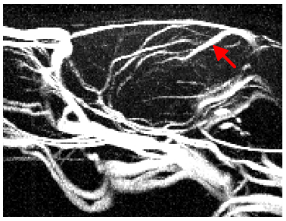

Fig. 3. Three dimensional MRA identified the large vessel (red arrow) which was dilated seen in figure 2.

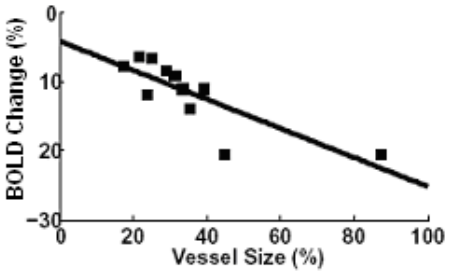

Fig. 4. A strong correlation between the negative BOLD change and the vessel size change (n=11, p=0.0026) was observed