# Cocaine-induced Cerebral ADC and Hemodynamic Changes Between Cocaine-naïve Rats and Rats with Repetitive Cocaine Treatment

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**Introduction:** It has been reported clinically that the chronic cocaine intake reduced the regional glucose metabolism in neocortical area, basal ganglia and the hippocampus[1] as well as reduced global and regional cerebral blood flow[2]. The mechanism underlying these cocaine-induced changes is still not fully understood. In vitro studies of canine cerebral vascular smooth muscle cells[3] have demonstrated that cocaine causes the cells to shrink to two-thirds of their original sizes. Other animal studies obtained by $^{31}$P NMR and angiography have further shown that cocaine induced vaso-constriction in both cerebral and peripheral vessels. We hypothesized that if repeated cocaine treatment induces vasoconstriction and reduced cerebral perfusion then the apparent diffusion coefficient (ADC) might also decrease. Here we use the diffusion-weighted MRI to study the ADC in living brains between cocaine-naïve rats and the rats with a repetitive cocaine treatment. Also, the peripheral homodynamic changes in response to an intravenous cocaine challenge are measured in a real time along with the MRI scan, including the heart rate and mean arterial blood pressure etc. to examine the temporal effect of the cocaine on cerebral ADC and the systematic hemodynamics in those animals.

**Material and Methods:** The Sprague-Dawley rats were used. In Group 1, rats received repeated administration of saline (0.8-0.9 ml) for 8-9 consecutive days though an intraperitoneal injection, whereas Group 2 rats received the administration of cocaine (20mg/kg/day) for that period. Before the experiment, the surgery was performed on the rat under isofluorane anesthesia (0.75-1.0% mixed with 2:1 air and oxygen gas). The femoral artery was cannulated for continuous blood pressure monitoring and tail and femoral veins for administrating an acute cocaine and $\alpha$-chloralose, respectively. After catheterization, the isofluorane was discontinued and a loading dose of 50mg/kg of $\alpha$-chloralose was administered followed by a continuous venous infusion of between 30-40 mg/kg/hr, titrated to stabilize the MABP at ~ 100 mmHg. For each of rats, the diffusion-weighted MR images (DWI) were acquired every 3-4 mins with an in-plane resolution of 0.3x0.3 mm, slice thickness of 1.8mm. TR/TE was 400ms/20ms and b-values were 125, 250, 400 and 1000 s/mm$^2$ (9.4T/20-cm horizontal magnet, Bruker). The rat was challenged by an acute cocaine administration (1mg/kg) through the intravenous vein during the experiment. All hemodynamic parameters were continuously measured during the experiments and the ADC changes in the cortical brain were assessed before and after the intravenous cocaine injection. In addition, the DWI was acquired for 10-15 min following euthanasia using overdose of anesthesia in Group 1 rats.

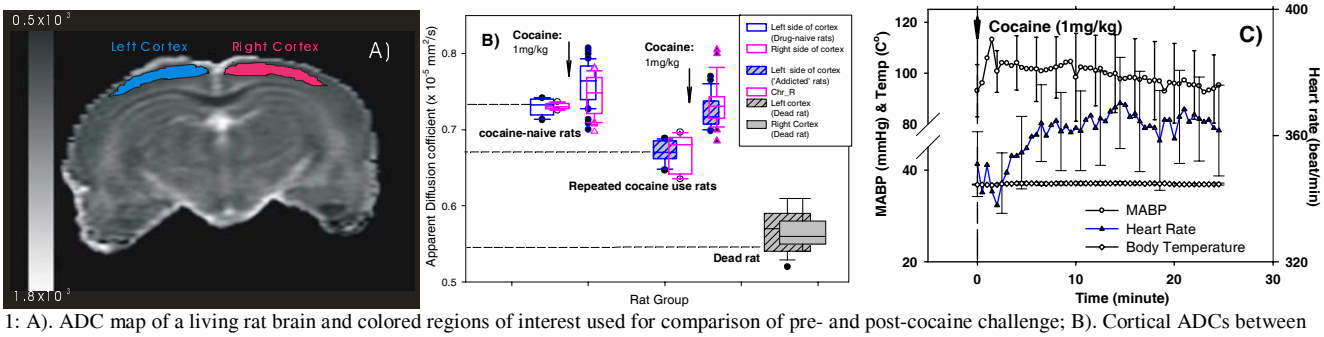


Fig 1: A). ADC map of a living rat brain and colored regions of interest used for comparison of pre- and post-cocaine challenge; B). Cortical ADCs between cocaine -naïve rats and the rats with repetitive cocaine treatment, and before and after cocaine challenge. Blue and Red boxes represent the ADCs in the left and right cortical regions of the brain, respectively. Grey boxes present the brain ADC of the rat following an overdose anesthetic euthanasia. C). Time courses of changes in the mean arterial blood pressure (MABP), heart rate and body temperature in response to the cocaine challenge during experiments.

**Results**: Fig.1B) summarized the cortical ADC values for the different group rats and their changes in response to an acute cocaine challenge. The ADC was decreased from 0.73±0.01 x 10$^{-3}$ mm$^2$/s in the cocaine-naïve rats (Group1) to 0.67±0.02 x 10$^{-3}$ mm$^2$/s in the rats with the repeated cocaine treatment (Group2), thus suggesting that cocaine exposure in 'chronic cocaine abuser' causes a longer lasting vasospasm which in certain areas may reach ischemic threshold levels (ADC's < 0.5 x 10$^{-3}$ mm$^2$/s). The insufficient decrease of ADC in dead rat brain (i.e., 0.56±0.02 x 10$^{-3}$ mm$^2$/s, shown in Fig.1B) might suggest that the micro-areas of ischemia in the cortex would not be directly detectable due to the volume averaging measurement applied. In addition, the acute cocaine challenge induced heart rate and mean arterial blood pressure to be increased in the rats as shown in Fig. 1C which are in agreement with the previous human studies demonstrated that cocaine abusers have decreased blood velocity and increased pulsatility in response to cocaine. This study advances our understanding of the advantages and limitations of the ADC technique applied to pharmacological studies.

**Reference:** 1). London et al., Arch Gen Psychiatry 47:567-74, 1990; 2) Johnson et al.,J Cereb Blood Flow Metab, 25:928-36 2005; 3) He GQ, et al, J Pharmacol Exp Ther 268(3):1532-9, 1994.