

Using ASL Method for Monitoring of Brain Perfusion Changes in a Rat Model of Schizophrenia and After Chronic Administration of Aripiprazole

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Abstract. *Animals prenatally exposed to polyriboinosinic–polyribocytidilic acid (poly I:C) can be used to parallel neuropathological abnormalities seen in schizophrenia patients. The aim of this study was to test the utility of Arterial Spin Labeling (ASL) MRI method for the evaluation of perfusion in different brain regions in the developmental poly I:C model of schizophrenia in rats. In these animals we further investigated the effect of chronic administration of the antipsychotic aripiprazole on brain perfusion. In the circle of Willis region, we observed significant ($p < 0,05$) increase of blood perfusion in the poly I:C model of schizophrenia in both males and females, and significantly higher perfusion in males than in females in vehicle-treated controls. Perfusion in hippocampus (in both hemispheres) was found significantly higher in males than in females in both vehicle-treated controls and poly I:C prenatally exposed animals. The significantly increased blood perfusion in the circle of Willis in poly I:C prenatally exposed males was found to persist even after chronic administration of aripiprazole. These results add new data to understanding of antipsychotic effects and demonstrate the viability of the proposed approach of combination of the ASL MRI method and the selected rat model of schizophrenia.*

Keywords: ASL, schizophrenia, poly I:C animal model, rats, aripiprazole

1. Introduction

Several animal models simulate schizophrenia pathologies. These models fit into four basic categories: pharmacological models, lesion-induced models, genetic models and developmental models. The poly I:C developmental model was used in this study. Poly I:C is used to mimic neonatal exposure to viral pathogens that can lead to alterations resembling brain changes in schizophrenic patients. Using the ASL MRI method we examined the perfusion changes in poly I:C model in rats. According to the finding of Nordquist et al. (2007) that acute administration of aripiprazole dose-dependently decreased brain activity in several brain regions, we also measured brain perfusion after chronic administration of aripiprazole.

2. Subject and Methods

Animal model

The developmental poly I:C model in rats was induced by acute subcutaneous dose of poly I:C (8 mg/kg) to 10 pregnant Wistar rat dams in the 15th day of their pregnancy. Vehicle was administered to 10 controls in the same time period. The adult offspring, both males (n = 6-11) and females (n = 5-10), were used for MRI measurements.

Chronic administration of aripiprazole

Adult rat males were divided into two groups. For one month, aripiprazole (5 mg/kg/day, orally) was administered to one group (n = 7-8), and vehicle (1ml/kg/day, orally) to the other (n = 8-9). All adult males underwent MRI measurements.

MRI acquisition

The rats were kept in general anesthesia using 2.0% isoflurane. Their respiration and ECG were controlled by the anesthesia level (to maintain 60 breaths per minute, 350±10 BMP) and the body temperature was stabilized to 37.7±0.1°C. Animals were monitored during the whole measurement.

MR imaging was performed in an experimental 9.4T MR scanner (Bruker Biospin 94/30 USR by Bruker, Ettlingen, Germany) using a receive-only 2×2 array surface coil (400 ARR R.BR) and a volume transmitter coil.

A RARE sequence was used to obtain anatomical images with the following acquisition parameters: TR/TE 3500/36.0 ms, image matrix 256×256, slice thickness 1.25 mm, 2D FOV 50.0×20.4 mm and RARE factor 2. An ASL sequence FAIR-RARE was used with the following parameters: TR/TE 10000/37.78 ms, image matrix 128×96, slice thickness 1.25 mm, 2D FOV 50.0×20.4 mm; from one axial slice through the brain a set of 15 magnitude images with TI of 30, 50, 100, 200, 300, 500, 700, 900, 1000, 1100, 1500, 1800, 2200, 2800, 3200 ms was used to calculate the tissue blood flow map.

Data analysis

All ASL data were analysed in ParaVision 5.1 (Bruker) , ASL blood flow maps were analyzed in manually drawn brain ROIs by own Matlab R2010a code. MRI data were analysed in STATISTICA (StatSoft. Inc.) software by the Mann-Whitney U nonparametric test (p<0.05).

3. Results

Ventricular enlargement was seen in poly I:C exposed rats as compared to vehicle-exposed rats (Fig. 1). Brain blood-flow maps were created from ASL images (Fig. 2). Brain perfusion maps analysed by Mann-Whitney U test; the resulting box plots are shown in Fig. 3-6.

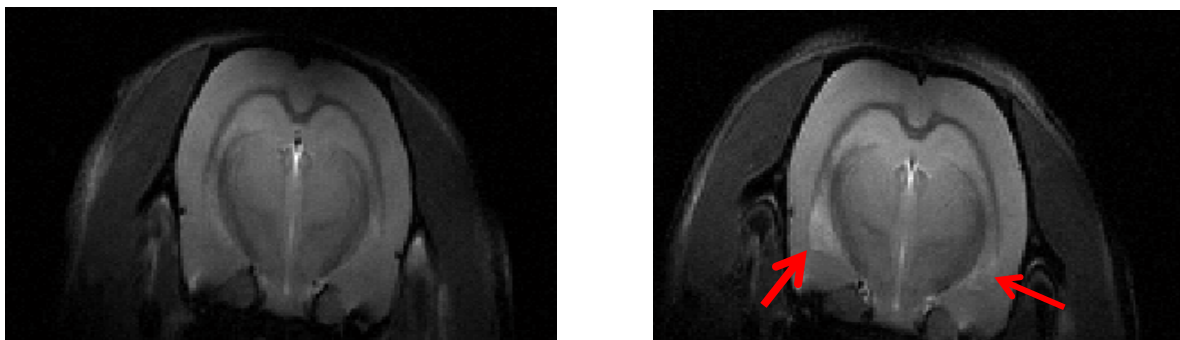


Fig. 1. Ventricular enlargement in a female rat prenatally exposed to poly I:C (right) versus a control, prenatally exposed to vehicle (left image).

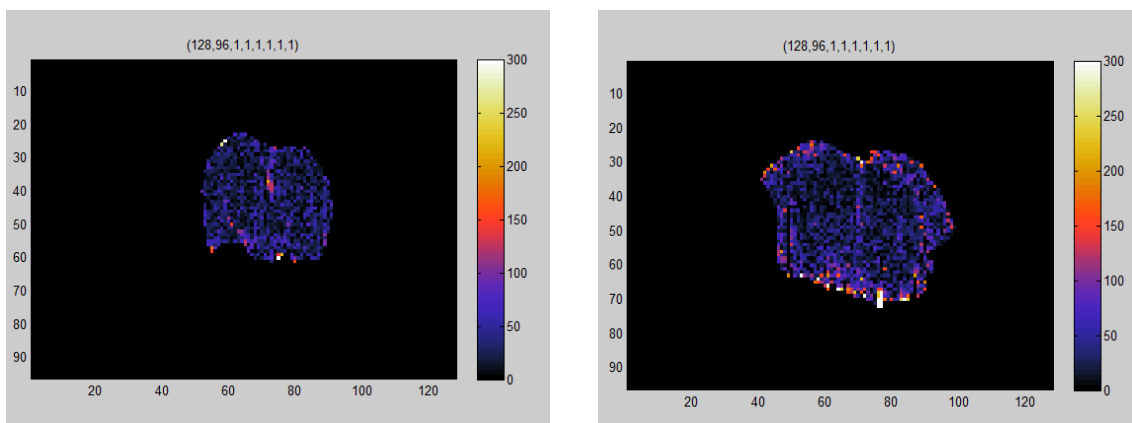


Fig. 2. Brain blood-flow maps created from ASL. A female rat prenatally exposed to vehicle (left image). A female rat prenatally exposed to poly I:C (right image).

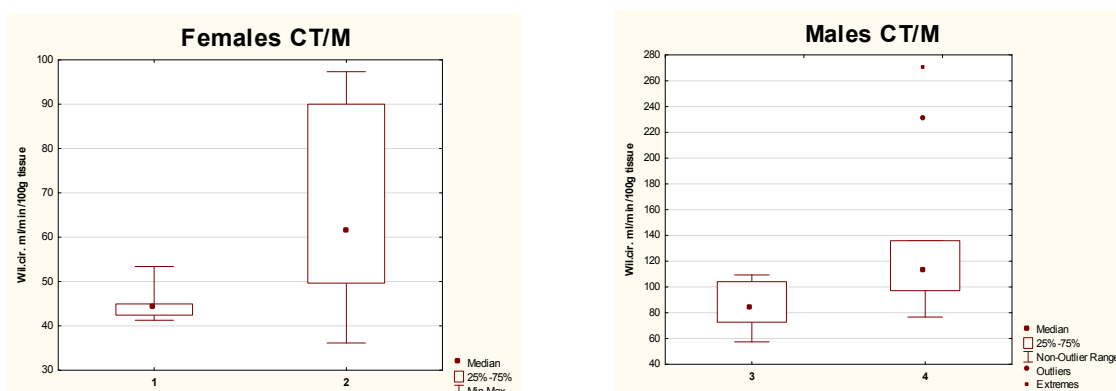


Fig. 3. Increased perfusion in the circle of Willis in rats prenatally exposed to vehicle (left column) / poly I:C (right column); females (left figure), males (right figure).

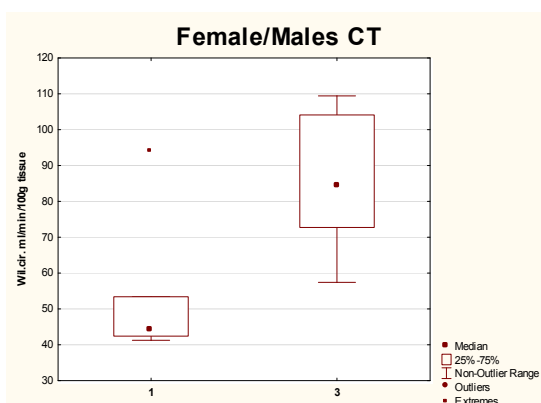


Fig. 4. Increased perfusion in the circle of Willis in vehicle-exposed male rats (right column) versus vehicle-exposed female rats (left column).

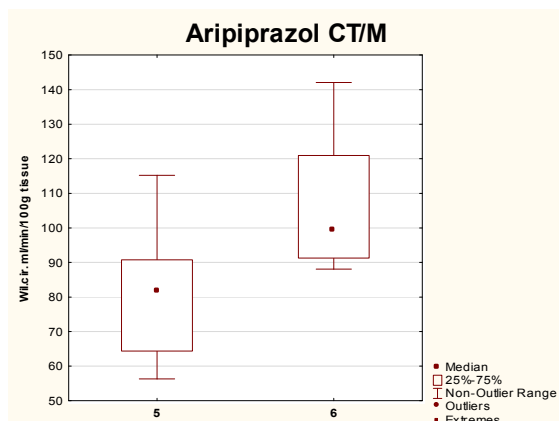


Fig. 5. Increased perfusion in the circle of Willis in male rats prenatally exposed to poly I:C (right column) versus vehicle (left column) in groups with chronic aripiprazole treatment.

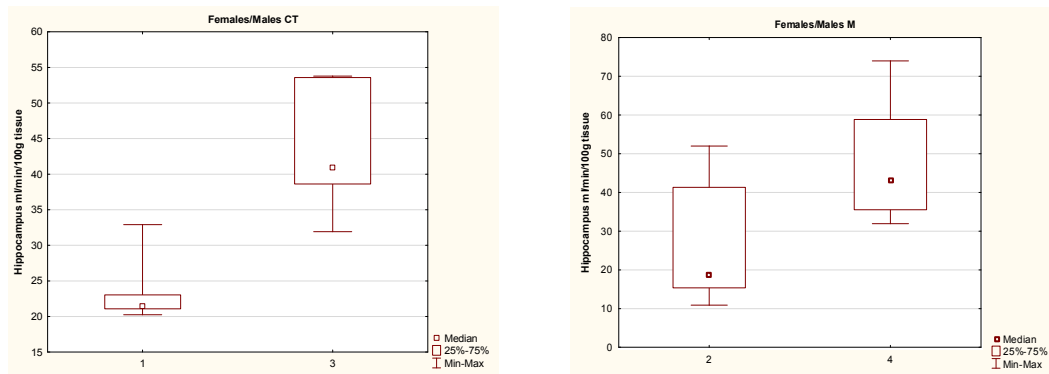


Fig. 6. Increased perfusion of hippocampus in rats prenatally exposed to vehicle (left figure) and poly I:C (right figure); females (left column) versus males (right column).

4. Discussion and Conclusion

We observed higher perfusion in the circle of Willis and hippocampus in male than in female rats. Furthermore, we found significantly increased perfusion in rats prenatally exposed to poly I:C in the circle of Willis region, which could explain the enlargement of lateral ventricles. These findings could be interpreted by an alteration of the dopaminergic system. Iadecola (1998) reported that dopamine profoundly influences all segments of cerebral circulation, and dopamine dysregulation is a hallmark of schizophrenia. *In situ* administration of dopamine produces vasoconstriction, but binding on D1 and D2 dopaminergic receptors induces vasodilation, hence increased perfusion. There was no evidence of aripiprazole effect on brain perfusion in male rats prenatally exposed to poly I:C. This can be explained by the fact that in humans, aripiprazole and its metabolite are partial agonists at D2 receptors, but its metabolite in rodents displays antagonist properties after a chronic administration [2]. Our results can further help in understanding of the mechanisms of antipsychotic effects. The combination of the ASL MRI method and the selected rat model of schizophrenia demonstrate a promising approach.

Acknowledgements

This work was partially supported by ACIU LM2011017, MŠMT (projekt. č. CZ.1.05/2.1.00/01.0017), MUNI/A/1116/2014

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