Focused Ultrasound Enhanced Intranasal Delivery of Neurotrophic Factors Exhibit Neurorestorative Effects in Parkinson's Disease Mouse Model

Robin Ji[1], Morgan Smith[1], Vernice Jackson-Lewis[2], Serge Przedborski[2,3], Elisa Konofagou[1,4]
[1]Biomedical Engineering, Columbia University, New York, NY, United States, [2]Pathology & Cell Biology, Columbia University, United States, [3]Neurology, Columbia University, United States, [4]Radiology, Columbia University, United States

Background, Motivation, and Objective:

Focused ultrasound enhanced intranasal (IN+FUS) delivery is a unique, noninvasive approach that utilizes the olfactory pathway to administer drugs directly to the brain. Drugs that typically do not cross the BBB, or have short circulating half-life, can now gain direct access to targeted brain regions. Our group has shown that IN+FUS delivery of model drugs provide a more homogenous distribution of delivery when compared to IN delivery alone, and similar delivery efficiency to intravenous delivery after FUS induced BBB opening. The aim of this study was to investigate the delivery efficacy and therapeutic effects of IN+FUS administered brain-derived neurotrophic factor (BDNF) has on an early stage Parkinsonian mouse model.

Statement of Contribution/Methods:

Wild-type mice were given a sub-acute dose of the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxin daily for 5 days, causing bilateral degeneration of the nigrostriatal dopaminergic pathway. After a stabilizing period, the mice were split into a treated group and a control group (N=7/group). The treated group was dosed with IN+FUS of BDNF weekly for 3 weeks. Each week, 0.4 mg of BDNF was intranasally delivered followed by BBB opening in the left substantia nigra (SN) and caudate putamen (CP) using FUS and sized isolated microbubbles. After the 3rd week, the mice were survived for 2 months to allow for any neurorestorative effects to occur. Then behavioral testing through amphetamine-induced rotations was conducted. Brains were harvested via transcardial perfusions and sectioned coronally. Staining of tyrosine hydroxylase positive (TH+) neurons in the SN and terminals in the CP were used to assess the nigrostriatal dopaminergic pathway integrity.

Results/Discussion:

Initial TH+ staining in the CP suggests a trend of greater staining in the ipsilateral side in treated mice (Fig. 1A) and similar staining bilaterally in control mice (Fig. 1B). Significant ipsilateral rotation in treated mice corroborate the initial TH+ staining (Fig. 1C), suggesting improved ipsilateral nigrostriatal dopaminergic pathway. These initial findings indicate a modest neurorestorative effect of IN+FUS BDNF on MPTP mice, demonstrating the potential of an alternative and efficient drug delivery route for brain treatment with FUS. Further TH+ staining and quantification in the SN and CP are ongoing to confirm these findings.

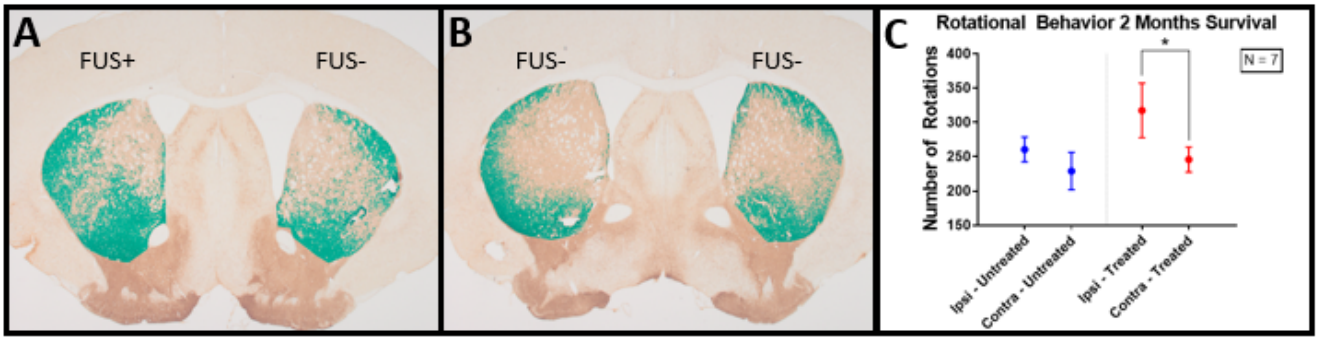

Fig. 1: (A) TH+ neurons in the CP of IN+FUS BDNF treated MPTP mouse with only the left side sonicated. (B) TH+ neurons in the CP of an untreated MPTP mouse with no sonication on either side. (C) Amphetamine-induced behavioral tests show a significant rotational bias toward ipsilateral side in IN+FUS BDNF treated MPTP mice but not in untreated MPTP mice. The mean and standard error is plotted.

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