Epigenetic relationships with response to Mindfulness Based Stress Reduction for PTSD

Jeffrey R. Bishop1,2, Adam M. Lee, Lauren J. Mills3, Paul D. Thuras2,4, Christopher R. Erbes2,4, Melissa A. Polusny2,4, Gregory Lamberty2,4, Kelvin O. Lim2,4,5

Minnesota Veterans Affairs Health Care System; 5. Defense Veterans Brain Injury Center

Abstract

Background
Mindfulness Based Stress Reduction (MBSR) is an effective non-pharmacologic treatment for Veterans with PTSD. Extensive work has identified epigenetic factors related to PTSD disease risk and pathophysiology, but how these factors influence treatment response is unclear. Serotonin signaling and hypothalamic-pituitary-adrenal (HPA) axis functioning may be perturbed in PTSD and are molecular pathways targeted by treatments for PTSD. We compared methylation levels in functional regions of the serotonin transporter (SLC6A4/5HTT) and FKBP5 binding protein 5 (FKBP5) genes between responders and non-responders to MBSR.

Methods
Genomic DNA samples from veterans with PTSD who received MBSR as part of a previously conducted clinical trial were examined. Responders (n=11) and non-responders (n=11) (defined by ≥10pt improvement on PTSD Checklist total scores after 9 weeks of treatment were selected and matched for age, sex, race, childhood trauma, current smoking status, and medication exposure. A targeted next generation sequencing approach of bisulfite-converted DNA generating 300-500 reads per region examined methylation (CpG) sites ( chr17:28562752-28563675) in SLC6A4 previously associated with expression and depression outcomes as well as the FKBP5 Intron 7 region (chr6:35558312-35558806) identified as a functional regulator of glucocorticoid signaling. Percent methylation was compared between responders and non-responders at baseline (pre-MBSR treatment).

Additionally percent change in methylation from before to after treatment was compared between responders and non-responders.

Results
Methylation of the SLC6A4 shore region of the promoter at baseline was higher in non-responders vs responders at CpG_35558513 (F(1)=5.97, p=0.024) and CpG_35558710 (F(1)=8.56, p=0.008), both of which reside in previously described glucocorticoid response elements (GREs).

Conclusions
These findings highlight the potential importance of epigenetic factors in determining response to meditation treatment in PTSD. In this carefully matched sample of responders and non-responders to MBSR, baseline methylation as well as changes in methylation after treatment were examined. Baseline differences in SHTT methylation indicate that efficient serotonin signaling may be important for meditation to effectively reduce PTSD symptoms. Additionally, decreases in FKBP5 methylation indicative of normalizing stress-related pathways were observed after treatment in responders as compared to increases in non-responders. This suggests that effective meditation may positively modify stress-related pathways at the molecular level.

Discussion
This is the first study to examine methylation relationships with treatment response to MBSR in veterans with PTSD who were carefully matched for other clinical and demographic variables. We observed that pre-treatment methylation patterns in a region of the SLC6A4 promoter were different in those who went on to respond or not respond to MBSR. Additionally we identified methylation changes in relation to treatment response in two FKBP5 GREs after 8 weeks of MBSR. These findings highlight the potential importance of the serotonergic system in moderating the response to meditation and the potential biological effects of meditation on genes which regulate HPA axis function.

Acknowledgments and Disclosures
This material is the result of work supported with resources and the use of facilities at the Minneapolis VA Health Care System, and the University of Minnesota College of Pharmacy Department of Experimental and Clinical Pharmacology, Minneapolis, Minnesota. The clinical intervention research was supported by VA grant 101C000063-01 to Dr. Lim.