Published in final edited form as:
Psychiatr Genet. 2014 August ; 24(4): 181–182. doi:10.1097/YPG.0000000000000039.

Examining the Utility of Using Genotype and Functional Biology in a Clinical Pharmacology Trial: Pilot Testing Dopamine β-Hydroxylase, Norepinephrine, and PTSD

David P. Graham, MD, MS[1,2,3], **David A. Nielsen, PhD**[1,2], **Thomas R. Kosten, MD**[1,2], **Lori L. Davis, MD**[4,5], **Mark B. Hamner, MD**[6], **Iouri Makotkine, MD**[7,8], and **Rachel Yehuda, PhD**[7,8]

[1]Neurorehabilitation: Neurons to Networks Traumatic Brain Injury Center of Excellence, Michael E. DeBakey Veterans Affairs (VA) Medical Center (MEDVAMC), Houston, Texas, USA.

[2]Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Texas, USA.

[3]South Central Mental Illness, Research, Education and Clinical Center (MIRECC), Department of Veterans Affairs, USA.

[4]Tuscaloosa VA Medical Center (TVAMC), Tuscaloosa, Alabama, USA.

[5]University of Alabama School of Medicine, Birmingham, AL

[6]Ralph H. Johnson VA Medical Center (RHJVAMC), Charleston, South Carolina, USA.

[7]James J. Peters VA Medical Center (JJPVAMC) Department of Psychiatry, Bronx, New York, USA.

[8]Ichan School of Medicine at Mount Sinai, New York, New York, USA

One of the major clinical problems faced in treating posttraumatic stress disorder (PTSD) is that no single treatment is effective for every individual. With the efficacy of medications being questioned (Ipser and Stein, 2012) and the suggestion that evidence-based psychotherapies reduce rather than remit PTSD symptoms (Steenkamp and Litz, 2013), finding ways to predict who may positively respond to a particular treatment is imperative to mitigate PTSD's negative consequences.

The dopamine β-hydroxylase (*DBH*) gene has a functional polymorphism, rs1611115 (known as -1021C->T or C-970T), with higher plasma activity being associated with the CC genotype in Veterans without versus those with PTSD, while the DβH activity was similar among T allele genotype Veterans, with the CC genotype having overall greater activity than the T carrier genotypes (Mustapic et al., 2007). This suggests PTSD attenuates DβH activity in the higher functioning CC genotype but not in the lower functioning T carrier genotypes; possibly representing a compensatory response to prolonged PTSD hyperarousal.

Corresponding Author: David P. Graham, MD, Michael E. DeBakey VAMC, 2002 Holcombe Blvd (153-TBI), Building 100, STE 2B-126A, Houston, TX 77030, USA, Tel: (713) 791-1414 x24215; Fax: (713) 794-7623, david.graham@va.gov.

Nepicastat is a potent, competitive, and selective DβH inhibitor selected for study because it decreases norepinephrine (NE) more potently and specifically than disulfiram (Stanley et al., 1997). Nepicastat, like disulfiram, should reduce the abnormally high NE activity generally found in PTSD and result in reduced PTSD hyper-arousal symptoms. The purpose of this study was to compare the utility of using genetics versus functional NE biology to predict who may respond to nepicastat.

This was a 6-week randomized, double-blind, multi-site, placebo-controlled study involving 22 OEF/OIF Veterans with PTSD, approved by each site's IRB and R&D Committees. Measures included the Clinician Administered PTSD Scale – D (hyperarousal) subscale (*CAPS-D*), *DBH* genotype, and 24-hour urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) sulfate form representing intra-neuronal noradrenergic metabolism (Filser et al., 1988). All participants who returned for at least one post-randomization visit (12 nepicastat and 10 placebo) were included in the intent-to-treat analysis. The primary efficacy measurement was the change in *CAPS-D* scores from pre- to post-treatment with the last observation carried forward. Sample consisted of 14 CC and 8 T carriers, was 45.5% White, 54.5% African-American. Alpha was retained at .05.

The two treatment groups did not differ for any demographic or psychiatric co-morbid condition, or genotype (all $P \geq .080$). Using a pre-post treatment repeated measure ANCOVA, controlling for ethnicity, we identified no direct treatment effect ($P = .567$) but did find a significant *DBH* genotype effect ($P = .020$) with the CC genotype showing greater change than the T carrier genotypes. There was no treatment by genotype interaction ($P = .584$). In comparison, there were no correlations between the MHPG-sulfate values and *CAPS-D* scores, whether examined pre-treatment, post-treatment, or for pre-post treatment changes ($P > .05$).

Our findings suggest that a functional genetic marker for *DBH* may be more useful than using state-dependent measures of noradrenergic activity for predicting an individual's change in PSTD symptomatology. More generally, our results suggest further investigation is warranted to determine if using specific genetic polymorphisms are more useful than functional biologic measures in predicting an individual's response to other targeted interventions.

Acknowledgments

The views expressed in this article are those of the author(s) and do not necessarily reflect the views, position, or policy of the Department of Veterans Affairs, the South Central MIRECC, the United States government, Baylor College of Medicine, University of Alabama School of Medicine, or Mount Sinai School of Medicine. This material is based upon work supported (or supported in part) by the US Army Medical Research Acquisitions Activity (USAMRAA), Department of Defense, and the VA Medical Centers Research and Development Services, Rehabilitation Research and Development Service Career Development Award-2 (Grant # B7496W), by NIH/NIDA 5 P50 DA018197-05, through MD Anderson's Cancer Center Support Grant DA026120 NIH/NIDA DA026120, and the Toomim Family Fund. Nepicastat was provided by (Biotie Pharma, Finland).

REFERENCES

Filser JG, Spira J, Fischer M, Gattaz WF, Muller WE. The evaluation of 4-hydroxy-3-methoxyphenylglycol sulfate as a possible marker of central norepinephrine turnover. Studies in healthy volunteers and depressed patients. J Psychiatr Res. 1988; 22:171–181. [PubMed: 2852249]

Ipser JC, Stein DJ. Evidence-based pharmacotherapy of post-traumatic stress disorder (PTSD). Int J Neuropsychopharmacol. 2012; 15:825–840. [PubMed: 21798109]

Mustapic M, Pivac N, Kozaric-Kovacic D, Dezeljin M, Cubells JF, Muck-Seler D. Dopamine beta-hydroxylase (DBH) activity and-1021C/T polymorphism of DBH gene in combat-related post-traumatic stress disorder. Am J Med Genet B Neuropsychiatr Genet. 2007; 144B:1087–1089. [PubMed: 17853400]

Stanley WC, Li B, Bonhaus DW, Johnson LG, Lee K, Porter S, et al. Catecholamine modulatory effects of nepicastat (RS-25560-197), a novel, potent and selective inhibitor of dopamine-beta-hydroxylase. Br J Pharmacol. 1997; 121:1803–1809. [PubMed: 9283721]

Steenkamp MM, Litz BT. Psychotherapy for military-related posttraumatic stress disorder: review of the evidence. Clin Psychol Rev. 2013; 33:45–53. [PubMed: 23123570]