

ABSTRACT

Background: There has been a growing recognition of the importance of epigenetic markers to PTSD. Epigenetic modifications are changes to the function (but not structure) of DNA that are caused by environmental exposures. Once in place, epigenetic modifications and (or 'marks') may impact posttranslational molecular mechanisms regulating stress responses relevant to the development of PTSD. Since these marks are thought to be enduring, they will not only provide information about PTSD pathophysiology, they will provide a valuable biomarker that will allow for the detection of PTSD and PTSD risk, and ultimately, its prevention and treatment. To date, there are no studies that are directly seeking to discover epigenetic markers in PTSD. It is imperative to include examination of epigenetic modifications in studies measuring biomarkers for PTSD and PTSD risk.

Specific Aims: To examine the extent to which an epigenetic marker – cytosine methylation of the human glucocorticoid receptor as measured on the lymphocyte – provides a relevant biomarker for PTSD. This will be accomplished by comparing cytosine methylation in combat veterans with and without PTSD. A second aim is to determine the association between cytosine methylation and the expression of glucocorticoid receptor related genes and splice variants of the human glucocorticoid receptor. Because we propose to measure cytosine methylation in the context of a large, multidisciplinary study (Biomarkers for PTSD, Charles Marmar, PI, Log Number 09284002) we also propose to examine the relationship between this epigenetic measure and other well-studied correlates of for PTSD.

Objective/Hypothesis: It is hypothesized that combat veterans with PTSD will demonstrate increased methylation of the GR gene in the specified location. Cytosine methylation status will also be associated with gene expression of two GR-related genes NR3C1 and FKBP5, as well as the 1F splice variant of the human glucocorticoid receptor. Cytosine methylation status will be significantly correlated with other functional measures of GR responsiveness being obtained in connection with the already approved protocol. These include the cortisol response to oral dexamethasone administration, GR binding on lymphocytes, and 24-hr urinary cortisol excretion. That is, increased methylation status will be associated with lower cortisol levels following dexamethasone (e.g., a greater cortisol suppression to dexamethasone), a greater number of cytosolic GR receptors, and lower levels of mean 24-hr urinary cortisol.

Study Design: 25 OIF/OEF veterans with combat PTSD and 20 veterans matched for combat exposure, age, and gender will be recruited. Veterans will receive a comprehensive psychological assessment at the University of California, San Francisco. Bloods will be collected and lymphocytes will be isolated and shipped to the Mount Sinai School of Medicine (Dr. Yehuda's laboratory). DNA and RNA will be extracted and subjected to methylation analysis and analysis of gene expression as described. Data will be analyzed using analysis of variance or covariance, as necessary and correlational and partial correlational analyses will be performed.

Relevance: This work investigates the utility of measure that is not only likely to be a valid biomarker of PTSD, but also one that will provide information about persons who may be at risk for the development of PTSD. Indeed, in animals who have been exposed to some kinds of early experiences, methylation of the GR occurs during a critical window in development. In humans, this window for this developmental effect is not known, but may predate young adulthood (when combat exposure occurs). Should this turn out to be the case, this marker may prove, in future studies, to be related to PTSD risk, and may ultimately be used in the context of screening for PTSD risk even prior to deployment. Although methylation changes are enduring, they are not permanent, in that under some circumstances, they be reversed. Thus, if this biomarker is associated with PTSD

risk, it might be possible to develop prophylactic treatments so as to minimize the risk of PTSD in response to trauma exposure.