Overview/Abstract

Prevalence rates for post-traumatic stress disorder (PTSD) and other fear and anxiety-based disorders are nearly twice as high for women as they are for men. Dysregulated fear learning, in particular excessive fear expression, is a core feature of PTSD. Non-human animal studies are key to identifying the neurobiological mechanisms involved in excessive fear expression, however much of the prior research employing animal models has used only males as subjects. If we hope to fully understand disorders of fear, experiments investigating the underlying neurobiological mechanisms of fear expression are needed in which females are studied. If such studies are not completed, the mechanisms will remain undiscovered and treatments for fear-based disorders, which are often informed by basic knowledge of fear learning processes, will continue to be grounded in studies largely done in males.

Fear expression can be studied in the laboratory using Pavlovian fear conditioning, a form of associative learning in which a neutral cue signals an aversive stimulus (e.g. mild shock). One such form of fear conditioning involves an association between an aversive shock and the context (i.e. place) in which shock occurs. The expression of this so-called contextual fear is assessed by later returning the animals to the place where shock occurred while measuring behavioral responses, such as freezing behavior or potentiation of the acoustic startle response, both of which are indicative of a state of fear. A recent study from my lab showed that males and females differ in the expression of contextual fear when freezing behavior was measured, however higher levels of fear were observed in females when potentiation of the acoustic startle reflex was measured. _The long-term goal of this project is to determine if this sex difference in the expression of fear requires the differential engagement of specific neural circuits._ Achieving this long-term goal will depend on the procurement of funds from the National Institutes of Health. We are at a critical point in this project and to move forward and be competitive for federal funding it is essential that we acquire data demonstrating the feasibility of the approach that will be used. The purpose of this OVPR seed grant proposal is to provide support for acquiring these data.

The proposed project will focus on completed two sets of studies which will provide the foundation for the to-be-submitted NIH R01. The first set experiments are designed to demonstrate that we can successfully employ fluorescently-tagged viral tracers to retrograde label specific neurons in the central nucleus of the amygdala following injections into either the ventral periaqueductal gray matter (vPAG; the brain region that drives freezing behavior) or the nucleus reticularis pontis caudalis (PnC; the region that drives fear-potentiated startle). Then we will combine the viral tracing with behavioral testing and molecular indicators of neural activity to determine whether specific populations of neurons in the central amygdala, either those that project to the vPAG or those that project to the PnC, are differentially activated in male and female rats by the expression of contextual fear. The second set of studies will provide critical feasibility and technical data for another approach that we will use in our to-be-submitted NIH R01. Here we will establish the effective parameters which will allow us to use 'designer receptors specifically activated by designer drugs' (DREADDs) to manipulate neural activity in those specific cells in the central amygdala that project to either the vPAG or those that project to the PnC. Obtaining these data will allow us to propose studies in which we use this method to manipulate activity in these circuits and test their effect on the expression of contextual fear.

Upon completion of this project, we will have strong evidence that we can use a multi-faceted approach to assess the function of specific neural circuits in the expression of fear and we will be ideally positioned to apply for and obtain R01 funding from the National Institutes of Health.