Preventing post-traumatic stress disorder: Novel pharmacological approaches based on the neuroscience of fear

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Post-traumatic stress disorder (PTSD) is a prevalent, debilitating and sometimes deadly consequence of exposure to severe psychological trauma. Interventions are limited and new approaches to prevention and therapy are much needed. Given our knowledge of the memory consolidation that occurs in the aftermath of trauma experiences, timely intervention is thought to be paramount as it is in myocardial or cerebrovascular infarction. Thus, we are working towards interventional approaches in the emergency department or on the battlefield to prevent the long-term sequelae of PTSD.

In the past few years, technological advancements have allowed the observation and perturbation of the macrocircuits and microcircuits thought to underlie PTSD-related symptoms. These findings have evolved our understanding of the dysfunctional brain circuits underlying PTSD and provided translational knowledge about the condition, including insights into the mechanisms of risk and resilience.

Our lab has focused on the intersection of human genetics, neurobiology, postmortem biology, and mouse brain utilization to understand neural and molecular mechanisms of trauma memory consolidation. Our ultimate goal is to develop novel neurobiologically derived targets for the prevention of PTSD. In one promising avenue of research, we discovered that the Tac2 gene (TAC3 in humans), which is expressed in neurons specifically within the centromedial amygdala (CeM), is required for consolidating fear memories. Furthermore, the Tac2 product, neurokinin B (NkB), and its specific receptor, Nk3R, are also involved in the consolidation of fear memories. We showed that increasing Tac2 expression via lentiviral transduction in the CeM or via PTSD-like stress induction enhances fear consolidation. This effect is blocked by Nk3R antagonists. Concordantly, silencing of Tac2-expressing neurons in the CeM with DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) impairs fear consolidation.

Together, these studies provide a deeper understanding of the role of the Tac2 gene and the CeM in fear processing. We are working to translate this new knowledge into more successful, scientifically informed and rationally designed biomarker- and neurobiologically-driven interventions for disorders of fear regulation, including anxiety disorders and PTSD.

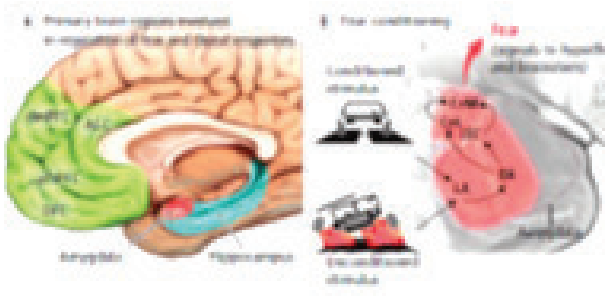

Fig. 1: Schematic of Trauma Memory Brain Circuits. A) The prefrontal cortex and hippocampus are the primary brain regions that regulate amygdala activity with fear/threat processing. B) Trauma exposure leads to synaptic plasticity events resulting in the consolidation of trauma memories within the amygdala, with the centromedial amygdala (CeM) as the primary output node eliciting the fear/threat reflex.

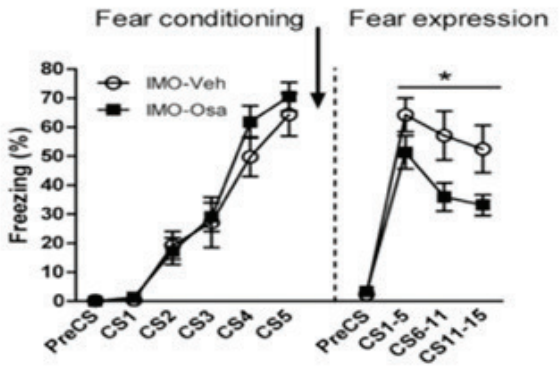

Fig. 2: Nk3R/TACR3 antagonist diminishes threat memory consolidation when given after threat exposure. Left) Acute stress/trauma model (foot shock in mice following immobilization stress) leads to fear memory responses (freezing). TACR3 antagonist is given up to 1 hour (systemically or within the CeM) after fear conditioning. Right) When tested on subsequent days, mice given osanetant (an Nk3R antagonist) exhibit diminished threat responses/freezing.