Public Abstract Kash / Holmes Proposal

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Exposure to stress is a major risk factor for many types of neuropsychiatric disease, and is a defining feature of Post-Traumatic Stress Disorder (PTSD). However, the risk for PTSD varies considerably between individuals, and different people can have very different reactions to even similar traumatic events. Indeed, while a significant proportion of soldiers serving in Operations Iraqi Freedom/Enduring Freedom exhibit symptoms of PTSD, many do not. This implies that some individuals are susceptible to the deleterious impact of stress, while others are resilient. Despite being the subject of enormous research efforts, the genetic and neurobiological factors that underlie stress susceptibility and resilience remain poorly understood. This is partly because studying these factors in human populations is extremely difficult given the myriad differences between individuals in brain function, genetics and life history. Animal models, and mouse models in particular, are an extremely powerful tool for studying the neural and molecular basis of stress susceptibility.

We recently discovered that two distinct genetic strains of mice differ in their behavioral responses to repeated daily exposure to a stressor (restraint). Following stress, one strain ('DBA/2J') developed a passive, anxious-like behavior when faced with threat, while another strain ('C57BL/6J') showed an active response. We found that these opposite coping responses were associated with marked differences in the pattern of gene activation in the amygdala, a critical brain region mediating stress and regulating emotion. Of particular note, genes encoding for the glutamate neurotransmitter system were differentially activated by stress in the two strains. This was an important observation because glutamate controls the excitability ('reactivity') and the plasticity ('adaptability') of the amygdala. Using electrophysiological recordings of neurons in the amygdala, we found that stress significantly altered the plasticity of amygdala neurons in the passive-coping DBA/2J strain such that neurons became over excited after stimulation. By contrast, the active-coping C57BL/6J strain was protected from these stress effects. Collectively, our preliminary study identified two mouse strains that differed in stress susceptibility and provided initial insight into the mechanism underlying these differences.

The current proposal will take these findings to the next level of analysis by studying the contribution of two major components of the glutamate system – the NMDA receptor and the kainate receptor. Both of these receptors were significantly altered by stress in the amygdala of the C57BL/6J strain. We will conduct a series of experiments to determine whether preventing these stress-induced changes prevents this strain from developing an active coping response. The results obtained would provide important new insight into the neurobiology of stress susceptibility and resilience. The wider implications would be that 1) at-risk soldiers could be screened for risk, via testing for at-risk gene variants and biomarkers, or neuroimaging for patterns of amygdala activation indicative of risk, 2) novel drug treatments could be developed that mitigate maladaptive reactions to trauma and even promote pro-active coping responses to stress. This proposal has the potential to significantly impact the prophylactic and palliative care of military populations.