ABSTRACT

Targeting AMPA receptor modulation following early life adversity: A mediator for threat associated memories

By

Roseanna M. Zanca

Advisor: Peter A. Serrano

Early life adversity (ELA) is the exposure to a single or multiple traumatic events before the age of 18 that go beyond the child's coping. These adverse events are often exacerbated during adolescence particularly when cognitive performance is compromised (REF). Adolescents who experienced ELA may show symptoms of post-traumatic stress disorder (PTSD), while not vividly recalling the early life trauma. These individuals show atypical connectivity between prefrontal-amygdala and hippocampus, all of which is associated with an increased risk of experiencing a traumatic event again later in life. While clinical research has increasingly expressed the importance in addressing the long-lasting consequences of ELA, treatment availability for ELA is low. Yet, animal models of the threat response during development have given clues into ways in which early adverse experiences transition later in life. Our previous research has provided behavioral evidence that there are differences in infant and juvenile threat processing's, reflecting age-specific wiring in the brain. However, research still lacks how molecular markers important for synaptic plasticity and memory are modulated across the development after threat exposure.

The overall GOAL of these studies was in identifying the role of AMPAr on transitional threat memory processing's at three ages of infancy, and between the juvenile and adult stage, to understand how the brain at different stages of life responds and processes threat.

Adult rats exposed to threat exhibit impaired long term memory retrieval for tasks learned prior to threat exposure. AMPAr and PKMζ expression, markers important for long term memory processing, are also dysregulated in acute and chronically threat exposed adults, suggesting threat memories may override or conflict with previously established memories. While previous research has provided evidence that synaptic plasticity is dysregulated in the adult brain after threat exposure, research still lacks how molecular markers important for synaptic plasticity and memory are modulated across development after threat exposure. Thus, the studies presented in this dissertation identified the role of threat associated AMPAr on developmental synaptic plasticity by *1. Utilization of age-specific threat conditioning paradigms 2. biochemical changes 3. influence of stress hormones. These experiments were done in identifying AMPAr as a mediator for early life adversity associated memories.*

To achieve this goal, two specific aims were carried out:

Specific Aim 1: Identify the role of AMPA receptor expression in the hippocampus and amygdala in threat memory retrieval during the juvenile or adult stage of life [Chapter 2]

Previous research on ELA early childhood trauma has focused primarily on the alterations of the developing amygdala-prefrontal circuitry, the hippocampus is also an important region in the threat circuit, where the contextual aspect of the threat memory is stored. While the amygdala has been shown to be involved in threat memories during the juvenile stage, the hippocampus is still a region yet to reach full maturation. Rats at this stage will demonstrate a threat response 24 hours later when tested in the initial training context, but; will not retain this threat memory as early as 4 days after the initial exposure. However, juvenile rats exposed to the initial context at 3 days and 6 days, recover a threat response,

suggesting consistent reconsolidation of memories in juveniles is needed for the sustainment of threat memories. This also suggests juveniles exhibit a failure to recall single threating events; something not seen in adult rodents. Studies focusing on the natural phenomena, infantile amnesia, the inability to maintain memories during infancy and early childhood, have considered possible reasons for forgetting and recall failure seen during this stage of development. Previous research shows that while adults and juveniles both have developed projections between the basolateral amygdala (BLA) and hippocampus, juveniles do not show activation of BLA to hippocampus projections during threat conditioning and extinction. This suggests the hippocampus and its projections to regions like the prefrontal cortex and amygdala are immature, making these immature projections a potential driving force behind increased forgetting in juveniles.

To identify the role of the AMPA receptor associated with threat memory retrieval in juvenile rats, we focus on both the amygdala and hippocampus in understanding how neural mechanisms important for threat memory processing's differentiate between juveniles and adults. Groups of male juvenile and adult rats were exposed to the pedestal stress paradigm and tested for contextual threat memory retrieval either 1d or 7d. Rats were sacrificed 30 minutes after test and the dorsal hippocampus and amygdala were evaluated for GluA1-3, PKMζ and PSD95.

We found that:

(1) Both juvenile and adults have intact threat memory retrieval 24 hours post-training. However, at 7 days post-training only adults exhibit a sustained threat memory
(2) GluA1-2 AMPAr subunits increase at 1d post-training in the Hippocampus of juvenile rats and phosphorylated Serine 845 GluA1 AMPAr subunit increases 7d post-training in the hippocampus of juvenile rats
(3) PSD-95 and phosphorylated Serine295 PSD-95 increase only 1d post-training in the amygdala and 7d post-training in the hippocampus of only adult rats

Overall, these results indicate long term dysregulation in the juvenile brain associated with adversity induced GluA1-AMPAr subunit expression. Additionally the increase in PSD-95 and its phosphorylated state observed only in adults, highlights the lack of mature dendritic spines and increased neurogenesis in juvenile seen in previous literature on infantile amnesia and ELA.

Specific Aim 2: Identify the role of AMPA receptor expression across in the amygdala in threat memory retrieval during infancy [Chapter 3]

Adolescents who have experienced maltreatment early in life respond faster to fearful facial expressions and show an overgeneralized threat response. This rapid response to these fearful facial expressions was also associated with activation of the prefrontal cortex, suggesting dysregulated development of the amygdala-prefrontal circuitry. Furthermore, longitudinal fMRI studies on adolescent individuals who experience ELA show atypical connectivity between the prefrontal cortex to amygdala and prefrontal cortex to hippocampus. This suggests that trauma has long term consequences resulting in atypical development of brains regions important for short and long term memory storage as well as emotional memory storage.

In rodents, altered connectivity between these brains regions is observed in models of maltreatment during infancy, resulting in depressive, anxiety like symptoms, and deficits in social behavior later on in adolescence. Furthermore, infant rats maltreated by the mother show increased levels of the stress hormone, corticosterone (CORT), suggesting CORT may play a role in the altered threat circuitry shown later in adolescent rats. Increasing CORT levels in the amygdala during infancy prematurely activates the amygdala threat circuitry, a function that usually does not emerge until PN10. With previous literature highlighting the effects of trauma on brain regions important for not only threat memory processing but also non-threat memory processing, this strongly suggests that altered and atypical development in these brain regions

may also serve as a driving force for the various impairments seen in trauma exposed adolescent youths.