Impact of adolescent social defeat stress on enduring cognitive effects from early life stress

Abstract

Both humans and rodents with a history of early life stress (ELS) display mild to moderate cognitive dysfunction and peer interaction deficits during adolescence. Here, we investigated how ELS can interact with subsequent social defeat stress (SDS) exposure in rats to lead to adult dysfunction. We exposed adolescent males with and without ELS to SDS in adolescence in order to model the impact of two “hits” to brain development. Cognitive function was assessed in adulthood using the win-shift working memory task, and social interaction was assessed using an open-field sociability task. We present here that adult rats display working memory deficits only if exposed to both ELS and SDS. We also tested the hypothesis that working memory deficits in adulthood will correlate with an enduring loss of neurons in the prefrontal cortex that are important for cognitive function. Together, these data demonstrate that two hits of stress are necessary for continued adulthood dysfunction.

Introduction

- Early life stress (ELS) exposure has been associated with an increased vulnerability to various psychopathologies that emerge in late adolescence, including substance use, schizophrenia and depression (Anda et al., 2008).
- ELS exposure reportedly decreases adolescent expression of the protein parvalbumin (PVB) in GABAergic interneurons of the prefrontal cortex (PFC) (Brehm et al., 2013).
- PVB loss has been associated with cognitive impairments and psychological disorders such as schizophrenia (Lewis et al., 2005).
- Behavioral consequences of ELS often result in human individuals experiencing social stress during adolescence (Fisher et al., 2012).
- Our lab has found that ELS-induced cognitive dysfunction and decreased levels of PVB are seen in adolescence but do not consistently endure into adulthood.
- This study used a maternal separation paradigm in conjunction with an adolescent social defeat stress (SDS) to test whether ELS-induced dysfunction seen in adolescence persists into adulthood.

Methods

Pregnant female multiparous Sprague-Dawley rats (250-275g) were ordered from Charles River Laboratories on day 15 of gestation. All experiments were performed in accordance to the 1996 Guide for the Care and Use of Laboratory Animals (NIH). At postnatal day (P)2, litters were randomly assigned to either the maternal separation early life stress (ELS) group or control (CON) group. Pups from the ELS group were individually isolated from their mothers for 4 hours per day between P2 and P20, and kept in a thermoneutral environment of 36 degrees. Rats were weaned at P21 and group-housed with same-sex littermates until experimentiation. At P40 (adolescence), they were again separated into either the social defeat stress (SDS) group or the no social defeat stress (no- SDS) group. The SDS male rats were placed into a cage with an aggressive dam that had just given birth. After five minutes or three submissive poses were observed by the adolescent, the two rats were separated by a mesh divider for thirty minutes. This was repeated for four days. At P90 (adulthood), they were tested for cognitive performance using the win-shift task. All animals were food restricted. Rats were habituated to an 8-arm radial maze on P90 and P91, then trained in the win-shift paradigm until criterion was reached (two consecutive days with <2 errors). After the animals reached criterion, they were tested using delays of 5min, 30 min and 3 hours in order to test their working memory. Once the animals had all completed win-shift testing, they were rapidly decapitated (~P85) and western blots were used to measure levels of PVB, normalized to β-actin.

Results

Social Defeat Stress Leads to Adult Working Memory Deficits in ELS-Exposed Animals

A. ELS leads to win-shift deficits in adolescence but not adulthood

B. ELS alone leads to PVB deficits in adolescence that do not endure into adulthood

C. Adolescent social defeat stress causes ELS-induced working memory deficits to endure into adulthood. 2-way ANOVA revealed a significant interaction between early stress condition and adolescent stress condition (F(1,11)=4.152; p<0.05). However, there were no main effects of either ELS or SDS on adult working memory performance.

Conclusions and Future Directions

- Preliminary findings indicate that animals that experience both ELS and SDS experience significant cognitive deficits in adulthood.
- Since there were no significant difference in levels of PVB between SDS animals and No-SDS animals using Western Blot current protocols are using immunohistochemistry in order to examine more subtle differences in PVB.
- Since many of the pathologies that are associated with ELS in humans involve social dysfunction, current protocols are examining the effect of SDS on adult social behaviors.
- Another component that is associated with stress is the release of Cortisol (CORT) in response to acute stress. There is evidence that ELS alters this stress response. Current protocols are using ELISA to examine CORT levels in response to an acute stressor in adulthood.

References

- Brehm HC, Andersen SL. Neuroscience and Behavioral Reviews 35:1687-1703 (2011)