Understanding the Link between Asthma and the Development of PTSD-like symptoms

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Introduction

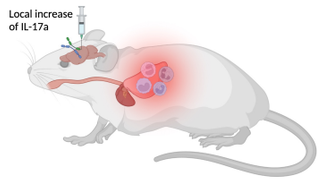
Background

PTSD/Asthma/IL17 association

- Post Traumatic Stress Disorder (PTSD) is a psychiatric condition, afflicting 4-7% of the US population (15-30% in war veterans).
- PTSD is characterized by increased fear, anxiety, and social avoidance following a traumatic experience.
- A higher prevalence of PTSD has been reported in individuals with severe asthma, characterized by a mixed Th2/Th17 response.
- Additionally, serum IL-17A has been seen to be elevated in patients with PTSD.

Purpose

- Previously, our lab reported PTSD-relevant fear extinction deficits in a model where lung inflammation was induced through House Dust Mite exposure, which increased IL-17a levels in the brain (Lewkowich et al 2020).
- To further understand CNS and PNS mechanisms, the purpose of this study was to investigate whether the localized increase in brain IL-17a concentration is sufficient to regulate PTSD-relevant behaviors.



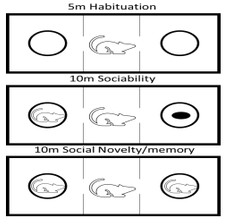
Hypothesis: Elevated IL-17a in the brain is sufficient for regulating PTSD-relevant behavior in mice and will alter neuronal activation within brain regions that regulate fear, anxiety and social behavior.

Methods

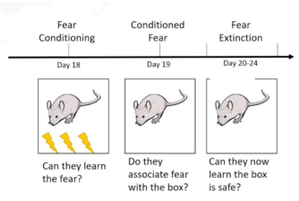
Experiment A (Behavior)
Subjects: 20 Male Balb/c mice implanted with cannulas
Injections: Experimental mice were given IL-17a, control mice were given artificial cerebrospinal fluid
Behavior: Anxiety like behavior was assessed in the Elevated Zero Maze, Sociability was assessed using the Social Interaction test, and Fear conditioning and Extinction Behavior was scored.

Mice were given injections **Intracerebroventricularly**

Elevated Zero Maze (time spent in the open arm areas was measured)



3-Chamber Social Interaction Paradigm (Interaction time measured)

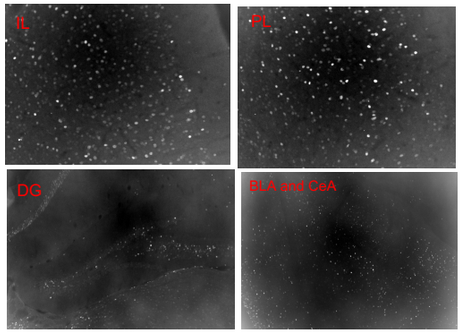


Fear Conditioning (Freezing Behavior was measured)

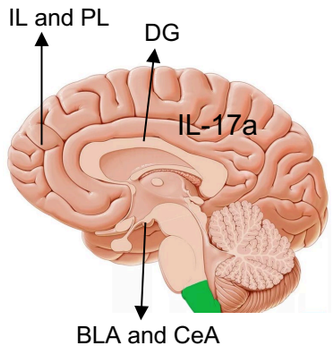
Experiment B (Immunohistochemistry)
Subjects: 16 Male Balb/c mice given injections of either IL-17a (8) or aCSF (8).
Immunohistochemistry: Brain tissue was collected 90 minutes after the last injection. cFOS, a marker for immediate early activation, was performed. Images were captured with a microscope and cells were counted using ImageJ. The Basolateral and Central Amygdala, the Infralimbic and Prelimbic cortex, and the Dentate Gyrus were quantified. Interregional and correlational analyses were also conducted, and heat maps were generated.

Results

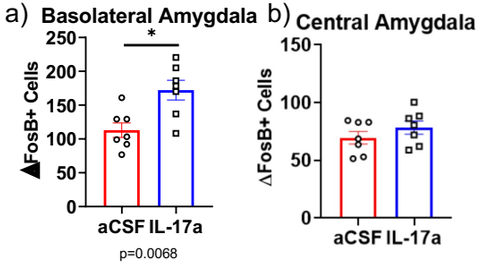
Experiment B: Immunohistochemistry

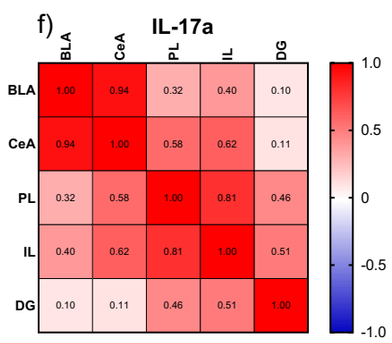


cFos labeled cells in IL-17a treated animals

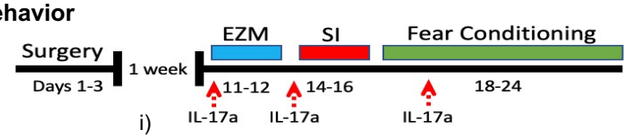


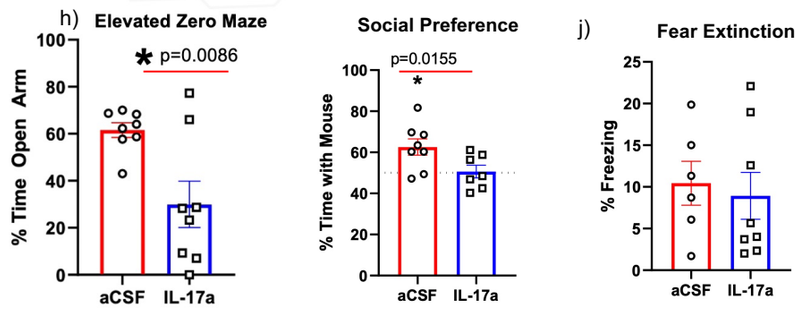
A significant difference was seen in the cells of the BLA (figure A) but not in any other regions (B-E). cFos interregional correlation matrices reveal that a correlation exists for the IL17-a animals between the CeA and the BLA (p=0.002) and between the PL and IL (p=0.027) (figure F). No difference was seen in the control group (figure G).





Experiment A: Behavior

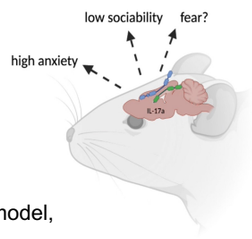




IL-17a treated mice exhibited significant reduction in open arm time in the EZM (figure H), which corresponds to anxiety like behavior, and reduced social preference in the Social Interaction test (figure I). No significant difference was observed in freezing during fear extinction (figure J).

Conclusions/ Future Directions

- This data provides novel information that increased IL-17a in the brain is sufficient to regulate anxiety and sociability behaviors relevant to PTSD. Altered activation in the basolateral amygdala and aberrant amygdala-prefrontal cortex activation patterns may contribute to these behaviors.



- Brain IL-17a may not be sufficient for regulating fear extinction deficits previously reported in an asthma model, and suggests peripheral contributory mechanisms
- Overall, the data reveals adverse behavioral effects of IL17a, an inflammatory cytokine associated with severe asthma. Beyond asthma, the data is relevant to other IL-17a- pathologies such as rheumatoid arthritis and airway inflammatory conditions such as COVID-19

The following must be investigated moving forward:

- Peripheral components and alternative injection timelines
- The role of Amygdala IL17a in anxiety and social behaviors
- Cellular phenotypes of activated neurons (excitatory or inhibitory)
- Understand the effect of sex differences, as females have a very different cytokine profiles and a higher incidences of PTSD

References

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Lewkowich, I., Ahlbrand, R., Johnson, E., McAlees, J., Nawreen, N., Raman, R., Lingel, I., Hargis, J., Hoover, C., & Sah, R. (2020). Modulation of fear behavior and neuroimmune alterations in house dust mite exposed a/J mice, a model of severe asthma. *Brain, Behavior, and Immunity*, *88*, 688–698. https://doi.org/10.1016/j.bbi.2020.04.084