The Role of the Endocannabinoid System in PTSD Early after Traumatic Injury

Terri deRoon-Cassini, PhD, Samantha Chesney, Karen Brasel, & Cecilia Hillard, PhD

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Quality of Life after Traumatic Injury

PTSD is a strong contributing factor to lower physical and emotional QoL after a traumatic injury

Kiely et al., (2008)
Quality of Life after Traumatic Injury

22% of survivors develop chronic PTSD after injury

PTSD is a strong contributing factor to lower physical and emotional QoL after a traumatic injury

Kiely et al., (2008)
Key Concept: PTSD

• PTSD = anxiety-related disorder that develops after trauma
  • Intrusive
  • Hyperarousal
  • Avoidance
  • Mood disturbance

• Impaired extinction of fear memories → intrusive recollections and re-experiencing of the original traumatic event (flashbacks or nightmares)

• Emotion dysregulation - Includes persistent alarm and distress, numbing, avoidance, increased arousal, as well as aberrant memory processes

Sripada et al, 2013
Neumeister et al, 2013
Sympathetic Nervous System Response

- Breathing rate increases
- Blood flow to skeletal muscles increases
- Intestinal muscles relax
- Heart rate increases
- Pupils dilate
- Blood pressure in arteries increases
- Blood sugar levels increase
More sustained changes

- Mediated by the hypothalamic-pituitary-adrenal system
  - Cortisol is released from the adrenal gland
  - Has widespread effects on the body

- Low acute cortisol has been linked with PTSD risk*
Stress-evoked changes are vital, but so is recovery to normal

- Sustained neuronal responses can lead to
  - Anxiety
  - Startle
  - Hypervigilance
  - Hyperarousal

- Sustained cortisol response can lead to
  - Sleep disturbances
  - Anxiety
  - Muddled thinking
  - Depressed mood
Emotion dysregulation evident early after trauma

deRoon-Cassini & Larson, 2014
Emotion dysregulation evident early after trauma
So what about a system that can respond to and buffer against the heightened stress response?
Endocannabinoid signaling system

**Background:**
- Endocannabinoid signaling system (ECSS)
Endocannabinoid signaling system

**Background:**

- Endocannabinoid signaling system (ECSS)
  - Neuromodulary system in CNS
  - Lipids (arachidonate based)
  - Enzymes
  - Receptors
Endocannabinoid signaling system

**Background:**
- Endocannabinoid signaling system (ECSS)
  - Neuromodulatory system in CNS
  - Lipids (arachidonate based)
  - Enzymes
  - Receptors (CB1)
  - **plays a regulatory role in response to stress by:**
    - Regulating amygdala activation and medial prefrontal cortical activity
Endocannabinoids are made in the body and activate CB1 receptor signaling.

Anandamide (AEA)

2-Arachidonoylglycerol (2-AG)
Endocannabinoid → CB1 receptor signaling opposes the effects of stress

- Reduce fear and anxiety
- Oppose sympathetic (fight or flight) response
- Increase drive to sleep
- Promote shut off of HPA axis following stress
eCBs, Anxiety, and PTSD

**Pre-clinical studies**
- CB1R Loss/inhibition potentiates anxiety-like behavioral responses to stress
- More endocannabinoids in the brain, less anxiety type behaviors
- CB1Rs are required for extinction of fear memories

**Human studies**
- Significant inverse relationship between circulating endocannabinoids and state anxiety
- Sample of 9/11 survivors, circulating 2-AG was significantly less in those with PTSD. (Hill et al., 2013)
CNR1 and FAAH Genes

rs806371 in CNR1
• CNR1 gene codes for the CB1 receptor
• Less CB1 receptor expression high levels of anxiety
• The rare allele (G) results in the formation of a regulatory site that inhibits CB1 receptor gene expression

rsrs324420 in FAAH
• Fatty acid amide hydrolase (FAAH) enzyme degrades AEA
• Increase FAAH results in decreased AEA and an increase in anxiety
• The rare allele for the FAHH gene (A) is associated with low FAAH and high AEA
PTSD with Level 1 Trauma Survivors

<table>
<thead>
<tr>
<th>Time since injury</th>
<th>PTSD Symptom</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo.</td>
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<tr>
<td>6 mo.</td>
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- Chronic distress: 21.8%
- Delayed distress: 5.6%
- Acute distress: 12.1%
- No distress: 60.5%

deRoon-Cassini, Mancini, Rusch, & Bonanno, 2010
Study on Trauma & Resilience

Study Aims:

1. Understand the role of AEA and 2-AG in the first 6 months after trauma

2. Determine differences in PTSD symptom severity across the genotype variants of the CNR1 and FAAH genes that might help to elucidate risk for PTSD
Study on Trauma & Resilience

Method:
• Longitudinal design
  • Hospital
  • Follow-up: 6 months
• Inclusion criteria
  • Admitted adult injured trauma patient
• Exclusion criteria
  • > mild TBI (GCS < 13)
  • Non-English speaking
  • Self inflicted injury

Procedure:
• Hospital: Blood draw (cortisol, 2AG, Anandamide, genetic analysis), PCL5
• 6 months: Blood draw, PCL5, CAPS
### Baseline (N = 278)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Mean Age (SD; range)</td>
<td>39.87 (15.64; 18-89.4)</td>
</tr>
<tr>
<td>Gender</td>
<td>72.3% Male</td>
</tr>
<tr>
<td>MOI – Assaultive?</td>
<td>67.3% Non-assaultive injury</td>
</tr>
<tr>
<td>Insurance?</td>
<td>82.7% Insured</td>
</tr>
<tr>
<td>Relationship status</td>
<td>58.6% In a committed relationship</td>
</tr>
<tr>
<td>TBI</td>
<td>98.6% Did not suffer mTBI</td>
</tr>
<tr>
<td>Mean ISS (SD; range)</td>
<td>10.37 (6.03; 0 - 34)</td>
</tr>
</tbody>
</table>

### Race (N = 278)

- Caucasian/White: 46%
- African American/Black: 45%
- Hispanic/Latino: 8%
- American Indian/Alaskan Native: 1%

### Highest Education Completed (N = 278)

- At least some college: 53%
- High school graduate: 27%
- Less than high school: 20%
Mechanism of Injury (N = 278)

- MVC: 33%
- GSW: 21%
- Fall: 17%
- Stab: 10%
- MCC: 7%
- Ped struck: 5%
- Other: 7%
- Crush/recreational injury: 5%
- Assault: 1%
- Other: 1%
Endocannabinoids and PTSD diagnosis
2-AG PTSD Diagnosis

- Levels of 2-AG are high acutely after trauma for all subjects
- For those who are PTSD positive at 6 months, trending significantly lower 2-AG
- No gender differences

<table>
<thead>
<tr>
<th></th>
<th>2-AG at hospitalization</th>
<th>2-AG at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD Negative</td>
<td>616.29</td>
<td>101.71</td>
</tr>
<tr>
<td>PTSD Positive</td>
<td>754.63</td>
<td>68.92</td>
</tr>
</tbody>
</table>

2-AG at 6-month follow up for PTSD Positive v. PTSD Negative: \( t(143.96) = 1.85; p = 0.06 \)
AEA and PTSD Diagnosis

- Higher AEA at baseline for those with PTSD at 6 months

Gender Differences
- For women, significant correlations between baseline and 6 month AEA and higher PTSD symptom severity in total and individual symptom clusters

<table>
<thead>
<tr>
<th></th>
<th>AEA at hospitalization</th>
<th>AEA at 6 months</th>
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</thead>
<tbody>
<tr>
<td>PTSD Negative</td>
<td>2.41</td>
<td>2.32</td>
</tr>
<tr>
<td>PTSD Positive</td>
<td>2.81</td>
<td>2.47</td>
</tr>
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</table>

AEA at baseline for PTSD Positive v. PTSD Negative:
\[ t(63.40) = 2.00; \ p = 0.050 \]
Are there differences in PTSD symptom severity for CNR1 and FAAH genes?
Genetic Variability in the eCB system and PTSD

† No significant differences in baseline PTSD symptom severity between genetic variants.

PTSD symptom severity at 6-month follow up for FAAH genetic variants: F(10,326) = 2.03; p = 0.30; partial $\eta^2 = 0.06$
A/A v. C/A: $p = 0.028$
A/A v. C/C: $p = 0.001$

No significant differences in PTSD symptoms across CNR1 receptor variants (all $p > 0.05$)
Summary

• Circulating endocannabinoids are relevant acutely after trauma, but quite opposite than what has been shown in the pre-clinical literature

• High levels of 2-AG are evident after trauma for all patients, but by 6 months lower 2-AG is trending in those with chronic PTSD

• AEA is significantly higher acutely in those with PTSD by 6 months
  • Animal literature has suggested a FAAH inhibitor could be beneficial, but based on these findings acute FAAH inhibition would not be indicated.

• Allele risk and protection may be related to the CNR1 and FAAH genes
  • And for FAAH in the acute aftermath of trauma, FAAH inhibitor may not be indicated

• 2-AG plays a role in chronic PTSD?
  • Is it about circulating 2-AG or ability of 2-AG to be recruited and maintained during stress after trauma
  • New findings regarding exercise and the ECSS
Future Directions

• What about pre-trauma ECSS functioning and risk for PTSD/system abnormal stress response?
  • Can bolstering the ECSS facilitate resilience in war fighters?

• Explore dense acute trajectories of 2-AG and AEA
  • Is there a switch, particularly for 2-AG or what is the optimal time for measuring eCBs in the acute time period after trauma

• Examine early life stress and differences in PTSD course

• Examine link between neural regions and circuits for emotion regulation and poor extinction retention early after trauma with eCB functioning to further develop phenotypes of risk

• Continue CNR1 and FAAH gene examination with chronic PTSD
Acknowledgments

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  NIH/NIMH, R01MH106574
  MCW Research Affairs Committee Grant
Can Marijuana use treat PTSD?
Can Marijuana use treat PTSD?
Exercise intervention and endocannabinoids
Contributions to PTSD

- Perception
- Emotion Regulation
- Fear Conditioning
- Amygdala & vmPFC dysregulation
- Endocannabinoid system
CB1 Receptor & Fear Extinction

• Animal Studies:
  • CB1 knockout mice (mice without CB1 receptor) learned and could recall the association between a tone and an electric shock
  • BUT, they were unable to extinguish this pairing despite elevated levels of endocannabinoids in the basolateral amygdala$^{1,2}$
  • Pharmacological blockade of CB1 also impaired extinction

1 Marsicano et al, 2002
2 Chhatwal et al, 2005
What About CB₁⁺ Agonism?

- Cannabinoid agonists, conversely, facilitated extinction in animal models of PTSD¹:
  - Agonist administration within 24h of exposure to stressful stimuli prevented the effects of a trauma
    - development of enhanced acoustic startle response, impaired extinction, and an altered neuroendocrine stress response, as compared with placebo administration²

¹ de Bitencourt et al, 2013
² Korem and Akirav, 2014
Endocannabinoids On Mood/Anxiety

• Treatment of obesity study:
  • Patients maintained on CB1 antagonists were >3 times more likely to discontinue treatment because of mood-related side effects (primarily anxiety) relative to placebo$^{1,2}$

→ Illustrates the role of endocannabinoids in mood regulation

$^1$ Christensen et al, 2007
$^2$ Moreira et al, 2009
Study on Trauma & Resilience
Preliminary findings

• Baseline – Assaultive versus non-assaultive trauma
So?

- Given that exposure therapy to treat PTSD is often associated with poor extinction retention,¹ these data suggest that cannabinoid administration during extinction training might reduce the reinstatement of fear responding.

¹ Milad et al, 2009
### 6-month follow-up (N = 172)

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<tr>
<th>Category</th>
<th>Value</th>
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<tbody>
<tr>
<td>Mean Age (SD; range)</td>
<td>42.79 (16.54; 18.1-89.4)</td>
</tr>
<tr>
<td>Gender</td>
<td>69.8% Male</td>
</tr>
<tr>
<td>MOI – Assaultive?</td>
<td>71.58% Non-assaultive injury</td>
</tr>
<tr>
<td>Insurance?</td>
<td>84.8% Insured</td>
</tr>
<tr>
<td>Relationship status</td>
<td>62.4% In a committed relationship</td>
</tr>
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<td>TBI</td>
<td>98.8% Did not suffer mTBI</td>
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<tr>
<td>Mean ISS (SD; range)</td>
<td>10.27 (6.13; 0 - 29)</td>
</tr>
<tr>
<td>Mean CAPS-5 Total Severity Score (SD; range)</td>
<td>13.55 (15.21; 0 - 62)</td>
</tr>
</tbody>
</table>

**Race (N = 172)**

- 48% Caucasian/White
- 43% African American/Black
- 8% Hispanic/Latino
- 1% American Indian/Alaskan Native

**Highest Education Completed (N = 172)**

- 57% At least some college
- 25% High school graduate
- 18% Less than high school
- 29% PTSD diagnosis based on CAPS at 6 months