Building Emotional Resilience: 
The Emerging Role of 
Cannabinoids for 
Mental Health & Emotional Pain

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Conflict of interest

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Stress
Terminology

**Hypothalamic-Pituitary-Adrenal (HPA) Axis**: Neuroendocrine central stress system, responsible for creation of cortisol. Also plays a role in mood, digestion, and immune function.

**Cortisol**: Primary stress hormone. End product of the HPA axis’ stress response.

**Endocannabinoid System (eCB or ECS)**: Our endogenous cannabinoid system, located diffusely throughout the body.

- "Almost all body processes can involve endocannabinoid signaling" - Piazza et al., 2017
- Helps us “relax, eat, sleep, forget, & protect” - Di Marzo et al., 1998

**Chronic pain**: Pain that lasts longer than 3-6 months, becomes its own disease state.
Cannabinoid Receptors: Both G protein-coupled receptors

- **CB1R**: Widespread, common in CNS, psychoactivity, pain relief, modulates neurotransmission throughout the body, responsible for THC “high”
- **CB2R**: Mainly on immune cells, anti-inflammation, muscle relaxant, less understood

Endocannabinoids: The body’s naturally occurring cannabinoids

- **AEA (Anandamide)**: Primarily activates central CB1, weak peripheral CB2
- **2-AG (2-Arachidonoylglycerol)**: Full agonist of CB1 & CB2, primary ligand of CB2

Phytocannabinoids: Primary cannabinoids present in cannabis sativa

- **THC**: Primary psychoactive component in cannabis. Effective in reducing pain, nausea, and inflammation. Increases appetite, anxiety at high doses. CB1R & CB2R agonist
- **CBD**: Non-intoxicating. Reduces THC-high, muscle tension, anxiety, and convulsions
1. First, a stressor causes the hypothalamus to release corticotropin-releasing factor (CRF).
2. CRF binds to receptors in the anterior pituitary gland, causing release of adrenocorticotropic hormone (ACTH).
3. ACTH binds to receptors in the adrenals (kidneys) that generate cortisol.
4. Cortisol finally acts back on the hypothalamus, downregulating the system and hopefully returning it to equilibrium. Negative feedback loop.
HPA axis dysfunction

- Prolonged and repeated stressors create a constant “fight or flight” response usually meant for short bursts
- Chronic stress weakens the immune system, strains the circulatory system, and puts constant cognitive strain on individuals
- Stress-induced dysregulation and sensitization of HPA axis similar across PTSD, chronic fatigue syndrome, chronic pain, fibromyalgia, and IBS
Understanding the problem:
Over 58 million Americans suffer from anxiety disorders

- Only 36.9% of this population seek and receive treatment
- 20% of American adults feel they do not do enough to manage their stress
- Gen Z and Millennials reported highest levels of stress
- Gen Z (youngest generation) most likely to report poor mental health

1 ADAA.org & US 2017 Census
2 APA: 2018 Stress in America survey
Standard-of-care treatments
Benzodiazepines

Increases effects of GABA, the primary inhibitory neurotransmitter, resulting in anxiety relief, muscle relaxation, and sedation

CBT, ACT, MBSR

Psychosocial treatments aimed at changing habits, beliefs, and behaviors of patients from the top-down

Antidepressants (SSRIs, SNRIs, etc)

Block reuptake of serotonin and/or norepinephrine to prolong and increase availability of both in synapses, lift mood, and decrease stress & anxiety
Is cannabinoid stress reduction a possible treatment option?
"There is wide consensus that ECS signaling generally reduces anxiety and fear responses.” - Piazza et al., 2017

Lutz et al., 2015
Moreira & Wotjak, 2010
Morena et al., 2016
Riebe & Wotjak, 2011
CB1 receptors are present throughout the HPA axis

Depending on the dosage, ratio, & situation, cannabinoids can be anxiolytic or anxiogenic

- Low doses of endocannabinoids dull stress, while high doses of ECBs increase stress
- Larger doses of THC => more anxiety

1 Rodríguez de Fonseca et al. 1996  
2 Martin et al., 2001  
3 Hilliard et al., 2018
ECS & stress

- We will see how eCB signaling generally reduces anxiety, fear responses, and provides buffering from chronic stress.
- eCB activity dulls anxiety in less stressful situations to help prevent chronic stress.
- During highly stressful stimuli, the ECS can increase anxiety responses.

Corcoran et al., 2015; Hohmann et al., 2005; Suplita et al., 2005; Valverde et al., 2000; Lutz et al., 2015; Dlugos et al, 2012; Hill et al, 2010; Moreira and Wotjak, 2009; Morena et al., 2016; Riebe and Wotjak, 2011
eCBs & stress

- Chronic stress reduces the # of CB1 receptors, although it can recover after a few days.
- Loss of CB1Rs is likely due to activation of glucocorticoid receptors, because a glucocorticoid antagonist (RU486) blocks reduction in CB1Rs.
- In all populations, lower levels of circulating AEA correlate with higher anxiety.

Morena et al., 2016; Rossi et al., 2008; Wamsteeker et al, 2010; Długos et al, 2012; Hill et al, 2008c
CB1 & the HPA axis

- eCBs regulate unnecessary glucocorticoid secretion in response to chronic homotypic stress
- This plays a protective role against developing chronic stress syndrome
- “In more general terms, the hypothesis can be put forward that the eCB system facilitates the activation of resilience factors during and/or after stress exposure.” - Russo et al., 2012
ECS at CB1 functions as stress-recovery system

- eCB system regulates habituation to homotypic stressors, not heterotypic ones
  - Homotypic Stressors: Stressors of the same variety vs. a barrage of many different kinds of stressors (ex: Marital problems, work problems, health, poverty)
- 2-AG release increased in response to repeated stress (Patel et al., 2005b, Rademacher et al., 2008)

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Patel & Hillard, 2008  
Patel et al., 2005b  
Rademacher et al., 2008
eCB system the “gatekeeper” of the HPA axis

- A disrupted endocannabinoid system is associated with failure to adapt to chronic stress
- Data suggests deficient eCB system may be implicated in affective disorders such as depression
- CB1 antagonists increase corticosterone secretion and enhance neuronal activity in the PVN, indicating higher stress responses in the HPA-axis
- Typical antidepressants have a downstream effect on eCB signaling in the limbic brain and that alteration contributes to their effectiveness

Gorzalka et al., 2008; Pi-Sunyer et al., 2006; van Gaal et al., 2005
Acute vs. chronic stress

- In response to acute stress, 2-AG levels do not tend to change much
- Repeated stress exposure, or chronic stress, causes an increase in 2-AG and downstream reduction in amygdala fear activity, driving habituation to stress.
  - A similar phenomenon happens in fear extinction, which has also been shown to be mediated by the ECS
Chronic stress conditions cause significant downregulation of CB1 and decreases 2-AG content in the hippocampus.

- This creates deficits in behavioral flexibility in rodents,
  - This signals a potential role in pervasive and unhealthy behaviors in mental health conditions including anxiety & depression.

Hill et al., 2005

Figure 2: Effect of 21 days of chronic stress on AEA and 2-AG content in the hippocampus (a) and limbic forebrain (b). *Significantly different from control (p < 0.05) (n = 5/group).
“Maintenance of positive adaptation (to stress) by individuals despite experiences of adversity”

Improvement in resilience correlated with stress & pain reduction

(Friborg et al., 2005; Luthar et al., 2000)
The endocannabinoid system in stress resilience
Cannabinoids & resilience

- eCBs regulate HPA axis’ long-term response to stress, improve coping, and improve stress habituation

- Deficient eCB systems increases risk of developing PTSD & depression

- CB1R agonists in vmPFC help reduce anxiety, fear expression, and active coping responses to stress.

Hill et al., 2009; Hillard et al., 2018, Martin et al., 2002; Bluett et al., 2017; Worley et al. 2017 ; Moldrich & Wenger, 2000, Worley et al., 2017
Evidence for cannabinoid treatment of pain & mental health
## Current evidence: cannabinoid treatment

### Mental illness & stress
- **Bergamaschi et al., 2011**: CBD reduces anxiety while public speaking in healthy naive individuals.
- **Greer et al., 2014**: Cannabis therapy effective in reducing symptoms for 75% of PTSD patients.
- **Phan et al., 2008**: THC dampens amygdala response to stress.

### Opioid dependence
- **Withdrawal symptoms relieved by cannabinoids**:
  - Anxiety, sleep problems, GI pain, nausea, & muscle pains
  - **Haroutounian et al., 2016**: 44% ↓ in opioid usage over 6 months with cannabis

### Pain
- **Lynch & Ware, 2015**: 7/11 controlled studies show **sig. pain ↓, QOL ↑** (sleep, anger, anxiety, and depression)
- **Degenhardt et al., 2015**: Cannabis + opioids > opioids alone for pain: ↑ QOL, ↓ pain, ↓ opioid usage
- **Agarwal et al., 2007**: Endogenous CB1 receptor (thus THC) primarily responsible for pain reduction

*Greer et al., 2014* define cannabis as a psychoactive substance used for its mind-altering effects, while *Haroutounian et al., 2016* research the effectiveness of cannabis in reducing withdrawal symptoms.

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The text discusses various studies on the effects of cannabinoid treatments, including reduced pain, improved quality of life (QOL), and benefits in mental health conditions. The studies highlight the potential therapeutic effects of cannabis in reducing withdrawal symptoms and pain, particularly in opioid dependence and mental health disorders.
Cannabinoid treatments for anxiety/stress

Chronic Stress
Cannabinoids help regulate the amount of unnecessary glucocorticoid secretion in response to chronic stress

Depression/anxiety
CBD shown to be effective as an anxiolytic
Deficient eCB system in patients with depression
QOL, incl. depression, improved with low THC cannabis

PTSD
Cannabinoid therapy effective in reducing symptoms for 75% of PTSD patients

Hill & Tasker, 2012; Hill et al., 2010, Greer et al., 2014; Ware et al., 2010; Bluett et al., 2017; Hohmann et al. 2005
The Opioid Epidemic
Understanding the problem:
Over 100 million Americans suffer from chronic pain

- Cannabinoids’ biochemically and neurologically reduce nociception
- Cannabinoids also improve secondary symptoms of pain likely to improve resilience.
  - This includes sleep disturbances, inflammation, nausea, anxiety, and depression, providing another novel opportunity for treatment

1 2016 National Survey on Drug Use and Health
2 Agarwal et al., 2007
3 Campbell et al., 2001; Haroutounian et al., 2016; Lynch & Ware, 2015; Martin-Sanchez et al., 2009
What is a modern definition of pain? Is it exclusively biomedical?
Pain is first sensed by nociceptors throughout the body.
- The signal travels through the spinal cord, crossing to the opposite side of the body.
- Afterwards, the signal travels through multiple lower levels of the brain until it is projected to the primary sensorimotor cortex via the thalamus.
- The limbic system mediates emotional and rewarding properties of pain.
- **Takeway**: pain is in and always from the brain.
- Nonetheless, biology alone cannot explain all of the variance in pain.
Pain is a biopsychosocial phenomenon:

Stress and anxiety shape the pain experience, especially when chronic

- Keefe et al., 1999
- Gatchel et al., 2007
- Turk et al., 2002
- Campbell et al., 2003
Medical cannabis as medicine, not recreation

Misconceptions:

- Not just another excuse to get high. The high is **not the point**
- Most medical doses do not need to cause prolonged intoxication, especially after tolerance is built
- “Sativa,” “indica,” and “hybrid” are a taxonomy that inadequately describe variance in cannabis
- THC-induced high and side effects can be reduced by including CBD
Cannabis dosing strategies for stress

- **Start low, go slow, stay low**
- Cannabis medicine is individualized; dose finding and adjustments are common
- CBD is consistently anxiolytic, doses of 5-10mg, starting once daily, up to 3x a day
- Lower amounts of THC can also be anxiolytic (1-5mg).
- Be sure to combine THC & CBD for maximal anxiety relief and attenuated high
- Tinctures & edibles for long-term relief (4-8 hours, 15-90 min onset), vaporization for immediate relief (2-4 hours, 5-10 min onset)
Future directions

- First and foremost, more research!
  - THC/CBD ratios for different conditions
  - Nature of “Entourage Effect” with terpenes, other cannabinoids (CBN, CBG, etc)
  - Long-term side effects
  - Drug interactions
- De-scheduling from Schedule 1 to allow for research of medical effects
- Integration with the healthcare system.
  - CME for doctors, healthcare professionals
  - Development of cannabinoid pharmaceuticals
  - Patient education
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References


