

Cannabinoids and Health

Module 9

Lecture 5: Cannabis and Anxiety and PTSD

Cannabis and Anxiety

- A systematic review of cannabis and anxiety from 2009 found that:
 - frequent cannabis users consistently have a high prevalence of anxiety disorders
 - patients with anxiety disorders have relatively high rates of cannabis use
 - unclear if cannabis use increases the risk of developing long term anxiety disorders
 - neurobiological, environmental and social influences need to be considered
- Precise relationship between cannabis and anxiety disorders not well understood

Cannabis and Anxiety Disorders

- A more recent systematic review (2018) of longitudinal studies on this topic found that:
 - Recent cannabis use associated with higher anxiety over time relative to comparison groups
 - Cannabis use associated with less symptomatic improvement after treatment
 - Recent cannabis use associated with negative long-term symptomatic and treatment outcomes
- However, findings should be interpreted with caution considering the samples (inpatients) and sources of cannabis consumed (unregulated sources)
 - So, 10 years later, we ***still*** lack a complete (or even basic) understanding of the association between cannabis and anxiety disorders!

Insights from the Endocannabinoid System

- Recent study examined relationship of circulating ECs (AEA and 2-AG) with affect and emotionality in 175 individuals with (n = 115) and without (n = 60) mood, anxiety, and/or personality disorders
- Circulating AEA levels had significant, inverse relationship with affect regulation
- Circulating ECs may play a role in emotionality across individuals regardless of defined psychiatric disorder

Can Modulating the eCB System Impact Anxiety in Humans? The Case for PTSD

- Preclinical and clinical data suggest that anxiety is associated with decreased endocannabinoid tone
- CB1 receptors in brain's fear circuit are crucially involved in the anxiolytic effects of cannabinoids
- Overall, the evidence suggests that targeting the endocannabinoid system may be an attractive and novel approach to the treatment of anxiety-related disorders
 - Particularly PTSD
 - But, need to determine whether benefits outweigh risks

Cannabis as a Treatment for Anxiety Disorders?

From National Academies Report:

- While there is a small association between anxiety and cannabis use disorder (CUD), anxiety does not seem to be a predisposing risk factor for developing CUD
- There is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders
- There is limited evidence (a single, small fair-quality trial) that THC (nabilone) is effective for improving symptoms of posttraumatic stress disorder

THC as a Treatment for Anxiety?

- Under specific conditions and at lower doses, THC has been shown to have anxiolytic, antidepressant and hypnotic effects in certain patient populations
- At higher doses THC has demonstrated the opposite effect, inducing panic, paranoia and anxiety in some subjects
- Chronic exposure to higher doses of THC may also have negative effects on anxiety

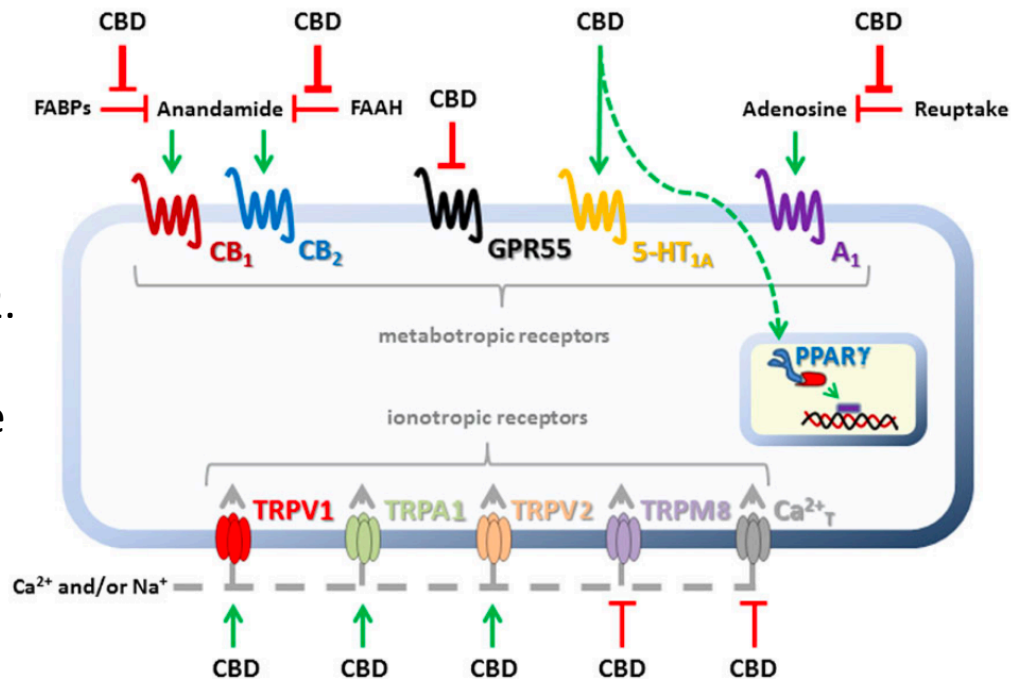
What about CBD in the treatment of Anxiety Disorders?

- Animal studies suggest CBD has anxiolytic properties
- A review of human studies (2015) found that CBD may be helpful for treating anxiety disorders
 - CBD reverses anxiogenic effects of THC
 - CBD reduces experimentally induced anxiety or fear
 - CBD reduced anxiety associated with a simulated public speaking test in healthy subjects and in social anxiety disorder
 - CBD enhanced extinction of fear memories in healthy volunteers
- Human studies supports anxiolytic role of CBD
 - currently limited to acute dosing
 - few studies in clinical populations

CBD as a Treatment for Anxiety?

- CBD reduces anxiety via 5-HT_{1A} and (indirect) cannabinoid receptor activation in paradigms assessing innate responses to threat
- CBD appears to regulate emotional memory processing in humans and in animal models

-CBD inhibits FAAH and FABPs
 -Results in indirect activation of CB₁ and/or CB₂
 -CBD also activates the 5-HT_{1A} receptor, PPAR_γ, TRPV1, TRPA1, TRPV2.
 -CBD inhibits adenosine reuptake and antagonizes GPR55, TRPM8 and T-type Ca²⁺ channels.
 5-HT_{1A} and (indirect) cannabinoid receptor activation are mechanisms that have been implicated in the anxiolytic effects of CBD



Lee et al., 2017, *British Journal of Pharmacology*

Cannabis and PTSD

- A big reason that PTSD patients seek out cannabis is that none of the treatments are very effective even after 90 day inpatient stay (Bonn-Miller, 2011)
- Another reason that is often cited by PTSD patients is sleep (Bonn-Miller, 2014)

CBD and PTSD

- CBD reduces cue-elicited fear responses in animals, probably through 5-HT_{1a} receptor
- CBD blocks reconsolidation of fear memory in animals
- CBD (32 mg inhaled) enhances fear extinction in humans (Das et al., 2013)
- CBD may also work because it has general anxiety reducing effect
- CBD may also help because it improves sleep
- Note: Lecture 6 is devoted to potential role of THC or THC+CBD in PTSD

Research/Treatment Challenges

- Majority of studies are on synthetic cannabinoids
 - not the plant, which is how most recreational and medical users consume cannabis
- Dosing and route of administration likely play an important role in the anxiogenic or anxiolytic effects of cannabis
 - but most studies to date have focused on a single, relatively low dose
- Insufficient evidence regarding long-term effects of chronic cannabis use on PTSD and other anxiety disorders
- Almost nothing is known about the combination of CBD and THC on anxiety

Summary

- Some studies suggest cannabis may make anxiety disorders worse
- Some studies suggest cannabis may make anxiety disorders better
- Details (dose, route of administration, level of CBD) probably make a difference but we do not have the research yet!
- Effects may also differ across anxiety disorders (e.g., GAD vs. PTSD)
- More evidence supports the anxiolytic effects of CBD as opposed to THC