

ENDOCANNABINOIDS AND PTSD SYMPTOMS

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Objectives

1. To review the effects of stress exposure on the body
2. To understand the relationship between THC from the cannabis plant and the endocannabinoid system of the brain
3. To learn about the role of endocannabinoid → CB1 receptor signaling in buffering the effects of stress

WHAT HAPPENS WHEN SOMEONE IS STRESSED?

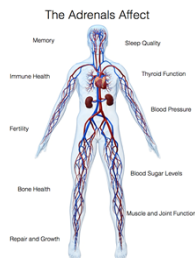
Immediate effects of stress

- Activation of the sympathetic nervous system
 - Increased heart rate and blood pressure
 - Increased blood flow to muscles, away from GI tract
 - GI muscles relax
 - Pupils dilate
 - Breathing rate increases



More sustained changes

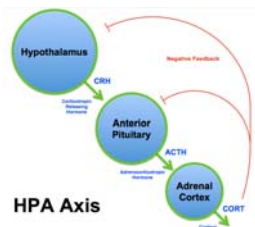
- Mediated by the hypothalamic-pituitary-adrenal system
 - Cortisol is released from the adrenal gland
 - Has widespread effects on the body



Stress-evoked changes are vital, but so is recovery to normal

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| <ul style="list-style-type: none"> • Sustained neuronal responses can lead to <ul style="list-style-type: none"> • Anxiety • Startle • Hypervigilance • Hyperarousal | <ul style="list-style-type: none"> • Sustained cortisol response can lead to <ul style="list-style-type: none"> • Sleep disturbances • Anxiety • Muddled thinking • Depressed mood |
|--|--|

The HPA response is turned off when cortisol is elevated

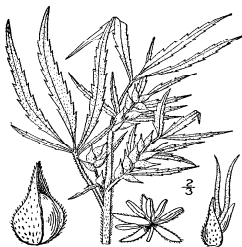


- If cortisol is increased to a high enough amount, the HPA axis is turned off
- When cortisol does not get high enough, it does not turn off

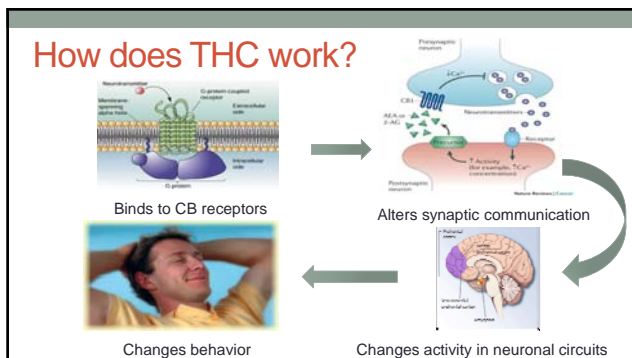
THC AND THE ENDOCANNABINOID SYSTEM

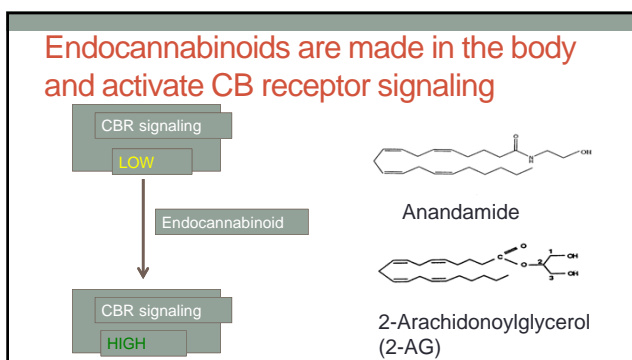
Acute effects of cannabis on humans

- Reduces feelings of stress and anxiety
- Elevates mood
- Alters sensory perception
- Alters short-term memory
- Causes sleepiness
- Increases appetite, particularly for "junk food"; increased fat storage



All caused by the chemical tetrahydrocannabinol (THC)





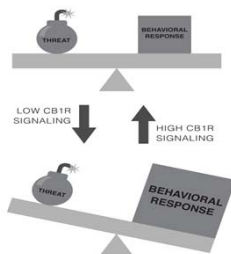
**ENDOCANNABINOID → CB1
IS A STRESS BUFFER**

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
- Reduce perception of pain
- Maintain hedonia (ability to feel pleasure)



Endocannabinoid → CB1 receptor signaling is essential for appropriate matching of behavioral response to threat

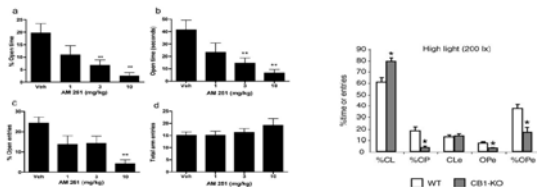


Stress and behavioral responses in rodents

- Avoidance of novel objects and places, reduced movement (freezing), hypervigilance, increased heart rate
- Commonly assessed using mazes that allow for choice between open (potentially dangerous) and closed (safe) spaces

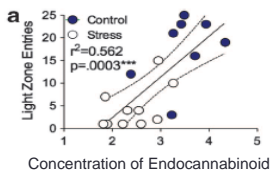


CB1R Loss/Inhibition Potentiates Anxiety-like Behavioral Responses to Stress



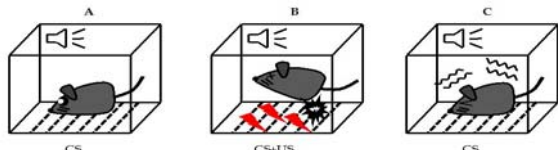
AM 251 is a CB1 receptor blocker

More endocannabinoid in the brain, less anxiety



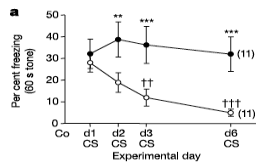
CB1 receptor is important for forgetting fearful memories

Studied in rodents using cued fear conditioning



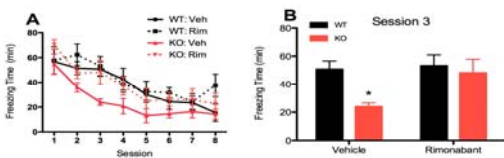
A. Mouse is given a tone; no effect
 B. A painful foot shock is given right after the tone; mouse freezes
 C. The tone is given the next day, the mouse freezes (remembers)

CB1Rs are required for extinction of fear



Wild type (open circles) exhibit reduction (extinction) of the fear response; CB1R^{-/-} (closed circles) mice do not

Mice with more CB1 receptors extinguish fear response more quickly



Red lines and bars are data from mice with about twice the amount of CB1 receptors in the amygdala

Basic studies show

- CB1R signaling is necessary for appropriate responses to a perceived threat and for appropriate extinction of aversive memories
- Elevation of CB1R signaling reduces anxiety and increases extinction of fear
- Humans use cannabis to self-medicate for anxiety and PTSD

Suggests the hypotheses that

- Reduced CB1R signaling is part of the etiology of stress-induced anxiety and risk for PTSD
- Elevation of endocannabinoid→CB1 receptor signaling mitigates the risk for developing PTSD, or the symptoms if it has occurred

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