Cannabinoid facilitation of exposure-based learning: A novel target to advance anxiety treatment

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Learning Objectives

• Understand how research uses extinction models to understand and study exposure-based therapies.

• Understand how the cannabinoid system is involved in extinction of fear memories.

• Discuss how the cannabinoid system may be a potential pharmacological target to enhance the learning during exposure sessions and what this may mean for advancements in treatment.

• Discuss the potential benefits and pitfalls of the cannabinoid system as a ‘cognitive enhancer’ for exposure-based therapies.
Background

- Anxiety Disorders
  - Failure to appropriately inhibit or extinguish fear
  - Exposure-based therapy
Background

- Pavlovian Fear Extinction
  - Models underlying dysfunction in anxiety disorders

Background

• Pavlovian Fear Extinction
  – Basic neural circuitry that regulates fear extinction
    • Ventromedial prefrontal cortex [vmPFC] and hippocampus [HIPP]
    • Dysfunctional in anxiety disorders

vmPFC = cognition; fear extinction recall
HIPP = memory formation; fear extinction recall
AMYG = emotional learning and responding
‘Healthy’ Fear Extinction Recall


A. Day 1 Conditioning
   - Shock
   - Extinction Learning

Day 2 Recall

Context Context with CS

B. Conditioning (CS+) – (CS-)
   - 8 CS+E
   - 8 CS+U

Extinction Recall (CS+E) – (CS+U)
   - Amygdala
   - Hippocampus
   - vmPFC

SCR (sqr)

% Signal Change

% Signal Change
PTSD and Impaired Fear Extinction Recall

• Deficient vmPFC-HPC during Extinction and Recall of Extinction Memory in PTSD

Milad et al. (2009). Biological Psychiatry, 66(12): 1075-82
• Pharmacological ‘Enhancers’ of Extinction Learning
  – Deletion of endocannabinoid CB1 receptors impairs extinction [Marsicano et al. 2002; Kamprath et al. 2006]
  – Extinction increases endocannabinoid levels (e.g. anandamide) [Marsicano et al. 2002]
  – Endocannabinoid-reuptake inhibitors facilitates extinction [Chhatwal et al. 2005]
  – Inhibition of endocannabinoid-degrading enzymes [e.g. FAAH] facilitates extinction [Gunduz-Cinar et al. 2012]

• However, the role of cannabinoids on the retention of extinction memory and its effect on the underlying neural circuits in humans is unknown.
Can cannabinoids facilitate fear extinction in humans?

Hypothesis: Pre-extinction administration of an acute dose of THC will facilitate extinction of conditioned fear responses compared to placebo (PBO) in humans.
Experimental Paradigm

Day 1
Fear Acquisition

Day 2
Extinction Learning
7.5 mg THC or PBO
120 min

Day 3
Extinction Memory Recall Test

8 x CS+E w/US
8 x CS+U w/US
15 x CS +E
15 x CS+U
15 x CS-

15 x CS +E
15 x CS-

20 x CS +E
20 x CS+U
20 x CS-

- Randomized, double-blind, placebo-controlled between-subjects design
- Acute pharmacological challenge of oral dronabinol [THC = 14] or placebo [PBO = 15] in healthy adult volunteers
Behavioral Results

THC does not affect within-session extinction learning to the CS+E

THC decreases SCRs to the CS+E compared to PBO
Summary of Behavioral Study

- Participants that had received PBO during extinction learning exhibited spontaneous recovery of fear to a CS that was previously extinguished (CS+E), whereas THC attenuated spontaneous recovery of fear.

- THC did not affect within-session extinction learning, but only influenced the ability to successfully recall extinction memory when compared to placebo, suggesting that THC affects the ability to maintain and/or successfully retrieve extinction memory.

Pre-extinction administration of THC facilitates extinction of conditioned fear in humans.

How does THC affect the underlying neural circuitry involved in fear extinction?
How does THC affect the underlying neural circuitry involved in fear extinction?

Cannabinoid modulation of prefrontal–limbic activation during fear extinction learning and recall in humans

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Hypotheses

Extinction Learning:
- During early extinction the CS+E will elicit conditioned fear responses (e.g. SCRs), but with continued presentations of the CS+E in the absence of the US SCRs to the CS+E will diminish.
- THC will not affect extinction of SCRs to the CS+E (versus CS-).
- During early extinction learning there will be AMYG activation to the CS+E (versus CS-). THC will not affect AMYG reactivity to the CS+E.

Extinction Recall:
- Relative to PBO, THC will decrease SCRs to the CS that was previously extinguished (CS+E).
- Relative to PBO, THC will enhance regional activation in the vmPFC and HIPP to the CS+E (versus CS+U).

Pre-extinction administration of THC enhances recall of fear extinction in healthy humans, which is mediated via increased activation and functional connectivity of the vmPFC and HIPP.
fMRI Experimental Paradigm

- Randomized, double-blind, placebo-controlled between-subjects design
- Acute pharmacological challenge of oral dronabinol [THC = 14] or placebo [PBO = 14] in healthy adult volunteers
- Functional data were processed and analyzed using SPM8
THC does not affect within-session extinction learning to the CS+E

Both groups demonstrated equivalent levels of extinction learning.
THC attenuates AMYG reactivity to the CS+E during early extinction.
No significant difference in SCR to the CS+E during extinction recall between PBO & THC

Both groups demonstrated successful extinction recall to the CS+E
THC increases regional activation in vmPFC & HIPP to the CS+E (CS+U) during extinction recall
Summary of fMRI Study

- THC did not affect within-session extinction learning, but did attenuate AMYG activation to the CS+E during early extinction.

- Both groups displayed significantly smaller SCRs to the CS+E compared to the CS+U during extinction recall; however, there was no significant difference between the THC and PBO groups.
  - THC may have reduced within group variability in extinction recall success

- THC increased regional activation within the vmPFC and the left HIPP and increased vmPFC-HIPP functional coupling to the CS+E (> CS+U) during extinction recall compared PBO.

--- Pre-extinction administration of THC modulates the underlying neural circuits involved in fear extinction in humans.
Can cannabinoids facilitate fear extinction?

- Maybe…
  - Conflicting behavioral results with the use of THC between our studies
    - Differential sensitivity to the effects of THC between individuals
    - ‘Floor Effect’
    - THC may not be effective in a non-clinical population (e.g. DCS studies)
    - Underpowered
    - SCR may not be sensitive to the effects of THC
    - Genetic influences**

Heitland et al. (2012). Translational Psychiatry, 2(e162)
Discussion

• Can cannabinoids facilitate fear extinction?
  – Maybe…
    • Conflicting behavioral results with the use of THC between our studies
      – Differential sensitivity to the effects of THC between individuals
      – ‘Floor Effect’
      – THC may not be effective in a non-clinical population (e.g. DCS studies)
      – Underpowered
      – SCR may not be sensitive to the effects of THC
      – Genetic influences**
    • Other cannabinoid compounds/targets
      – Cannabidiol (CBD)
      – Increase endocannabinoid levels rather than introducing exogenous compounds
Discussion

• Can we ‘rescue’ behavioral and neural deficits in fear extinction recall in PTSD with an acute dose of THC?

• Prompt investigation of the cannabinoid system as a pharmacological target in exposure

The goal of ‘cognitive enhancers’ is not to treat [physiological or subjective] symptoms of anxiety, but rather to serve as an adjunct to the exposure session and enhance the learning that takes place during a session.
• CBT is an effective, first-line behavioral treatment for anxiety disorders, so why do we need ‘cognitive enhancers’?

  – What are the benefits?

  – What are the potential pitfalls/considerations?
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