

The Role of Prefrontal Cortex CB1 Receptors in the Modulation of Fear Memory

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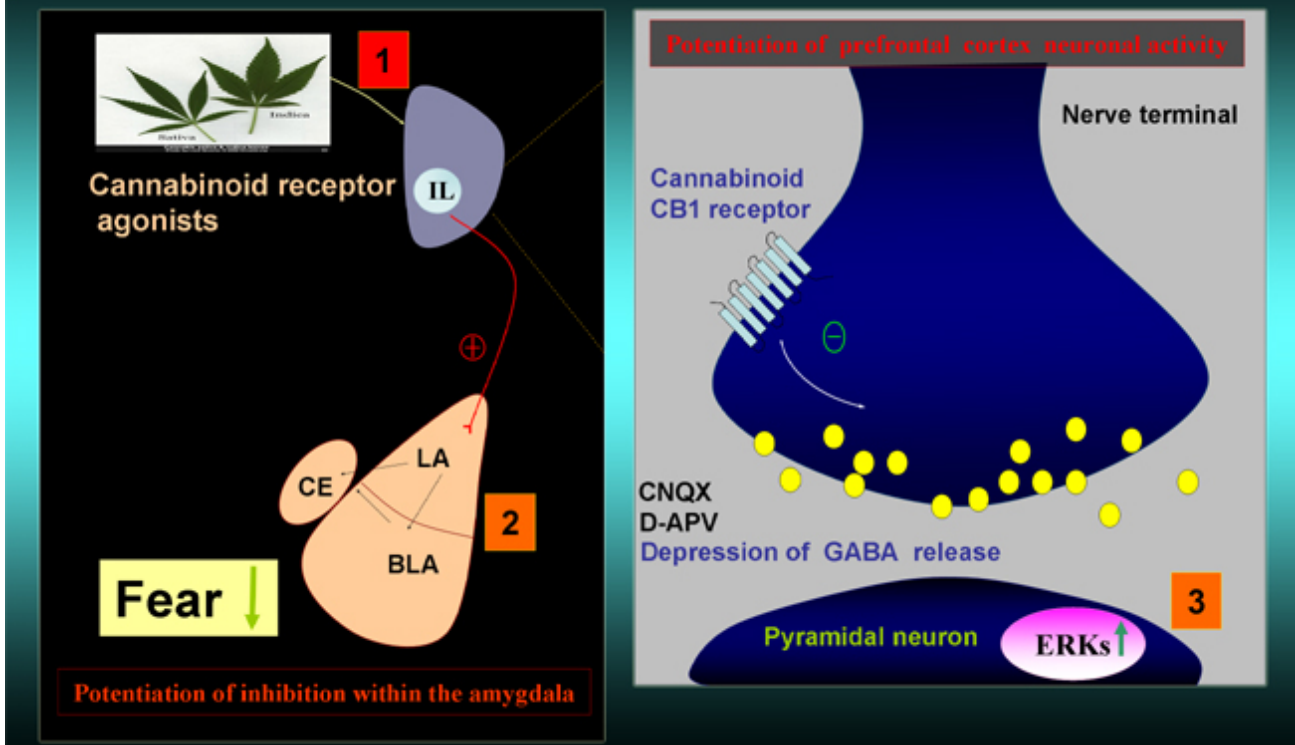
Cerebral Cortex 19:165-175, 2009.

Understanding the mechanism of how fear memory can be extinguished could provide potential therapeutic strategies for the treatment of posttraumatic stress disorders. Pavlovian fear conditioning is a behavioral procedure in which a cue (conditioned stimulus [CS]) induces a fear response when it is repeatedly paired with a noxious stimulus, often a footshock (unconditioned stimulus [US]). However, a conditioned response gradually disappears after animals are repeatedly exposed alone to the cue without the footshock, a process termed extinction. Studies of extinction in animals and humans indicate that the mPFC is critically involved in this behavioral process; however, the cellular mechanism of extinction within the mPFC remains to be defined. We determined whether the CB1 receptors within the mPFC play a critical role in the modulation of fear memory.



We have demonstrated that 1) preextinction infusion of the CB1 receptor antagonist into the IL blocked extinction; 2) infusion of a cannabinoid agonist into the mPFC before extinction training facilitated extinction of conditioned fear; 3) infusion of a cannabinoid agonist into the mPFC 24 h after training reduced fear-potentiated startle in the absence of extinction training; and 4) the effect of cannabinoid agonists was mimicked by an eCB uptake inhibitor and FAAH inhibitor. We have also demonstrated that activation of cannabinoid receptors in the mPFC induced ERKs phosphorylation. MEK inhibitor blocked the effect of cannabinoid agonists on the fear-potentiated startle at the same dose that inhibited cannabinoid agonist-induced ERK phosphorylation. In the present study, we suggest that cannabinoid receptors in the mPFC is involved in the extinction of fear memory.

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In conclusion, there are 3 important findings of this study. First, activation of CB1 receptors in the mPFC facilitates extinction. Second, cannabinoid agonists reduce fear-potentiated startle independent of conditioning stimulus. Third, activation of CB1 receptors in the IL induces ERKs phosphorylation. Cannabinoid receptors within the mPFC and the integrity of the mPFC--amygdala circuitry are important in the regulation of emotionally learned fear.

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