PPARα inhibition impairs the reconsolidation of fear memories in mice

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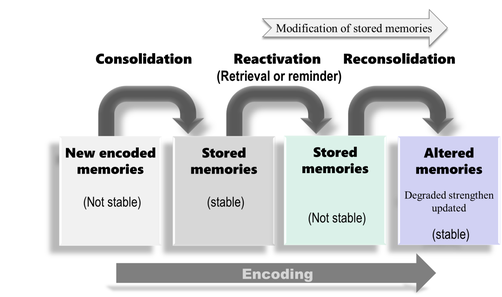
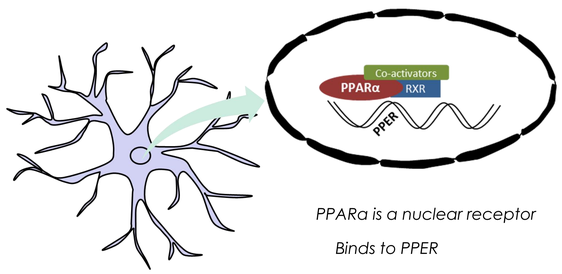
Introduction

Fear conditioning is the association of an initially neutral conditioned stimulus (CS) with an aversive unconditioned stimulus (US). Repeated pairing comes to elicit a conditioned response that reflects fear learning acquisition. Recently acquired fear memories strengthen over time and become more stable, a process known as memory consolidation. However, when an established memory is reactivated, it becomes labile to change and must undergo consolidation again (reconsolidation) to prevent extinction. Past studies suggest that both memory consolidation and reconsolidation require protein synthesis to be retained in long-term memory.

Endocannabinoids have been shown to be some of the neuromodulators of this process. Our lab's recent study revealed that inhibitory neurotransmission can drive the endocannabinoid degradation to promote memory consolidation. It was shown that fear conditioning accelerates the endocannabinoid 2-arachidonoyglycerol (2-AG) degradation and selectively elevates the 2-AG degrading enzyme monoacylglycerol (MAGL) levels in cerebellar lobule V/VI, a region involved in the consolidation of associative fear memory. The transcriptional factor peroxisome proliferator-activated receptor alpha (PPARα) binds to the promoter region and enhances the gene transcription of MAGL and recent findings from in vivo and in vitro studies supported this idea.



Encoded memories can be modified in a process of updating the new information available



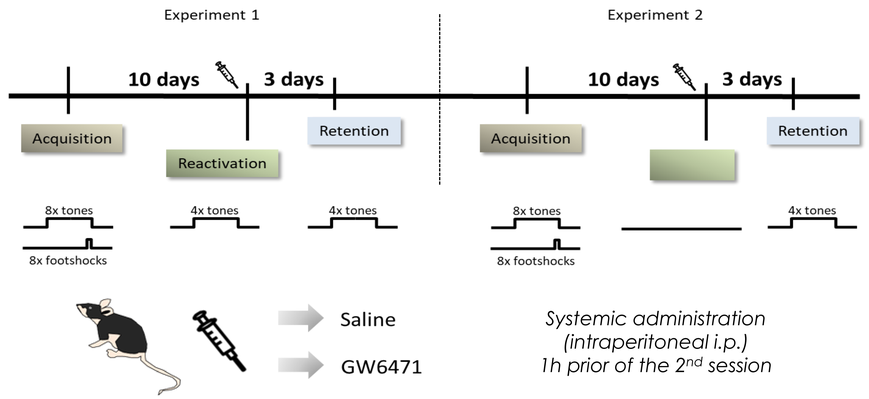
Neuron of the CNS

PPARα is a nuclear receptor

Binds to PPER

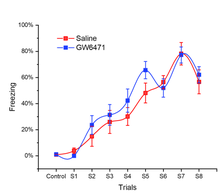
Acts as a transcriptional factor

Behavior Procedure

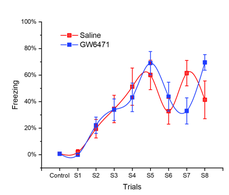


Fear Conditioning

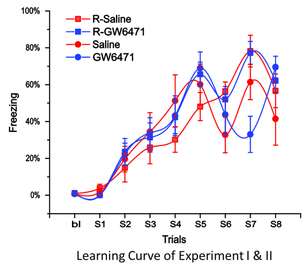
During the two minutes of acclimatization period (control) as expected animal did not freeze. After the pairing of the tone (CS) and the foot shock (US), gradually animal started freezing . We see an elevation in the freezing responses over time. We used the average freezing responses of the last three tones (S6-S8) to estimate the percent freezing during the session employed in this paradigm. Animals in all 4 groups learnt to associate tone to foot shock.



Learning Curve of Experiment I



Learning Curve of Experiment II



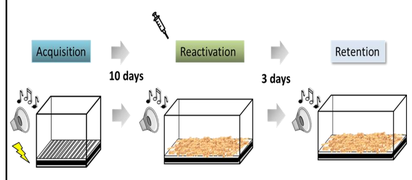
Learning Curve of Experiment I & II

During the acquisition phase

Experiment I Data

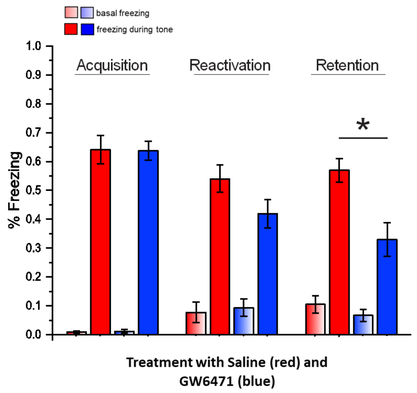
We found that the freezing responses evoked by the cue during the memory retention test were significantly reduced when mice were administered with PPARα antagonist prior to the reactivation session compared to the control mice that received a saline injection.

Fear conditioning consisted of three sessions: acquisition, reactivation, and retention



i.p. injections 1h prior the 2nd session

2mg/kg GW6471 or Saline

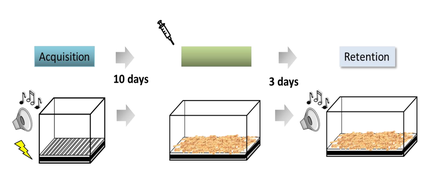


Treatment with Saline (red) and GW6471 (blue)

Experiment II Data

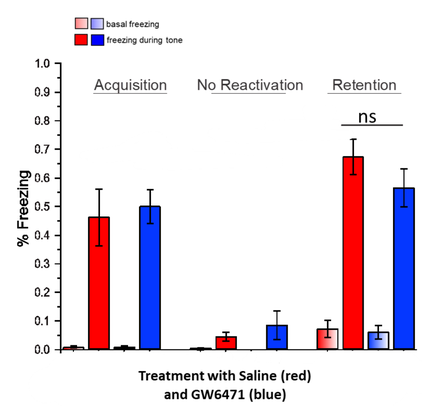
PPARα antagonist did not cause any effect in the freezing responses when the reactivation session was absent ten days after the fear acquisition. Inhibition of PPARα interfere with cue induced fear memories. Taken together, these findings suggest an impairment of the fear memory reconsolidation induced through the inhibition of the transcriptional factor PPARα.

Fear conditioning consisted of two sessions: acquisition and retention



i.p. injections 1h prior the 2nd session

2mg/kg GW6471 or Saline



Treatment with Saline (red) and GW6471 (blue)

Conclusions

- **We found that the freezing responses evoked by the cue during the memory retention test were significantly reduced when mice were administered with PPARα antagonist prior to the reactivation session compared to the control mice that received a saline injection.**
- **PPARα antagonist did not cause any effect in the freezing responses when the reactivation session was absent ten days after the fear acquisition. PPARα is required for the reconsolidation of associative fear memory.**
- **Taken together, these findings suggest an impairment of the fear memory reconsolidation induced through the inhibition of the transcriptional factor PPARα.**