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""PPARα inhibition impairs the reconsolidation of fear memories in mice"

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) can upregulate MAGL and recent findings from in vivo and in vitro studies in our lab supported this idea.

The scope of our study was to investigate whether the PPARα transcriptional factor has a role in the reconsolidation of fear memory. To this end, we examined the impact of PPARα on the freezing responses evoked by the pairing of the CS (75 dB tone) with an aversive US (0.75 mV foot shock). Systemic administration (intraperitoneal, i.p. 2mg/kg) of the PPARα antagonist, GW6471, in male adult mice was performed 1 hour before the reactivation session. The protocol of the fear conditioning we used consisted of three sessions: fear acquisition in context A (CS+US; Day 1), fear reactivation in context B (CS only; absence of CS; Day 11), and cued extinction memory retention in context B (CS only; Day 14). Contextual memory was tested in context B in the absence of the tone at day 11. We found that the freezing responses evoked by the cue during the extinction 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. Inhibition of PPARα neither interfere with contextual memory nor alter 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.