



Roflumilast enhances cannabidiol effects on fear memory reconsolidation through cAMP modulation

Poster

Comportamiento/Cognitivo - Behavioral/Cognitive

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Fear memory retrieval triggers reconsolidation or extinction in a time-dependent manner. Between these processes lies limbo, a period in which memory is insensitive to amnesic agents. Here, we investigated whether phosphodiesterase 4 (PDE4) inhibition modulates limbo, altering memory susceptibility to cannabidiol (CBD) treatment. Male Wistar rats underwent a 3-min re-exposure to the fear-conditioned context (retrieval 1), followed by treatment with roflumilast (PDE4 inhibitor; ROF, 0.1 mg/kg, i.p.) or vehicle (VEH). After 24h, animals underwent retrieval 2 to induce reconsolidation (3 min), limbo (10 min), or extinction (30 min), followed by CBD (10 mg/kg, i.p.) or VEH. After 1 and 10 days, we performed Tests A1 and A2, followed by the reinstatement test. We evaluated cAMP levels in fear-related brain regions after retrieval and ROF treatment, as well as in tissues treated with ROF in vitro. ROF, CBD, and the combination of both treatments impaired reconsolidation. ROF and CBD alone produced no effect when the limbo phase was assessed. However, associating both treatments reduced freezing behavior in all tests. When extinction was assessed, ROF treatment facilitated this process. In vivo, ROF increased cAMP in the prelimbic and amygdala, while reducing it in the ventral hippocampus. In vitro, ROF altered extracellular and intracellular cAMP levels across fear-related brain regions, indicating

that PDE4 inhibition modulates cAMP dynamics associated with fear memory processing. Together, the findings suggest that PDE4 modulates limbo. Inhibiting this enzyme increased the memory sensitivity to the CBD effect on reconsolidation. These effects engage the prelimbic and amygdala.

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