The involvement of cannabinoids and mTOR in the reconsolidation of an emotional memory in the hippocampal–amygdala-insular circuit

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Abstract
Memory reconsolidation is the process in which reactivated long-term memory becomes transiently sensitive to amnesic agents. We evaluated the ability of post reactivation administration of the mTOR inhibitor rapamycin, separately and in combination with the cannabinoid CB1/2 receptor agonist WIN55,212-2 (WIN), given systemically or specifically into the hippocampal CA1 area, basolateral amygdala (BLA) or insular cortex (IC), to reduce inhibitory avoidance fear in rats. Systemic administration of rapamycin after reactivation of fear memory impaired reconsolidation and facilitated extinction. A combined treatment with WIN and rapamycin resulted in similar effects. WIN injected systemically facilitated extinction, with no effect on reconsolidation. WIN alone and with rapamycin also decreased anxiety-like behavior. Further, when spontaneous recovery was tested, the WIN+rapamycin group did not demonstrate recovery of fear which can occur spontaneously after the passage of time. Rapamycin and WIN had differential effects on reconsolidation and extinction when microinjected into the CA1, BLA and IC. Furthermore, exposure to shock increased p70s6K activation in the BLA, indicating activation by mTOR. Treatment with rapamycin, WIN or WIN+rapamycin decreased activation and there was a strong positive correlation between fear retrieval and p70s6K activation in the BLA, suggesting that enhanced fear retrieval is associated with enhanced p70s6K activation. Taken together, the results suggest that rapamycin or a combined treatment that involves blocking mTOR and activating cannabinoids may be a promising pharmacological approach for the attenuation of reactivated emotional memories, and thus, it could represent a potential treatment strategy for disorders associated with traumatic memories.

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1. Introduction

A brief reactivation of a stabilized memory may trigger a second wave of memory consolidation termed reconsolidation (Nader et al., 2000). Pharmacological manipulation at memory reactivation can prevent or enhance the subsequent expression of the conditioned fear response (Lee et al., 2006).

Targeting the reconsolidation process may provide novel means of disrupting maladaptive memories in post-traumatic stress disorder (PTSD) (Schiller et al., 2010), persistently reducing symptoms of the disorder following only a single (or few) treatment sessions combining behavioral and pharmacological therapy.

The amygdala and the hippocampus have been demonstrated to be critical in fear memories reconsolidation (Baldi and Bucherelli, 2015). The insular cortex (IC) was found to be critical for the reconsolidation of conditioned taste aversion memory (Garcia-Delatorre et al., 2010). However, insular hyperactivity was consistently observed in PTSD patients (Etkin and Wager, 2007; Simmons et al., 2008).

mTOR is a serine/threonine kinase involved in synaptic plasticity and memory processes (Hoeffer and Klann, 2010), and through the formation of mTOR complex 1 (mTORC1), exerts a crucial role in the regulation of protein synthesis. The mTOR pathway regulates mRNA translation through its downstream targets p70S6 kinase (p70S6K) and the elongation factor 4E binding protein (Ma and Blenis, 2009).

The mTOR inhibitor rapamycin administered systemically or into the BLA or hippocampus after fear memory reactivation inhibited memory reconsolidation (Blundell et al., 2008; Jobim et al., 2012). In a study with PTSD patients, interference with the reconsolidation of fear memories with rapamycin ameliorated military-related psychological trauma symptoms in veterans with recent traumatic memories (Suri et al., 2013).

Animal and human studies have suggested that the endocannabinoid (eCB) system could represent a therapeutic target for the treatment of stress- and anxiety-related disorders such as PTSD (Fraser, 2009; Ganon-Elazar and Akirav, 2009, 2012; Korem and Akirav, 2014; Lutz, 2009; Patel et al., 2005; Rotman et al., 2014). Several studies focused on the role of the eCB system in reconsolidation with some conflicting results. Some studies found lack of effect on reconsolidation with a CB1 receptor antagonist administered post-reactivation (Kobilo et al., 2007; Suzuki et al., 2004). Others found that intra-amygdala post-reactivation injection of the cannabinoid agonists WIN55,212-2 and HU210 disrupted reconsolidation (Lin et al., 2006) whereas the fatty acid amide hydrolase inhibitor URB597 produced a small, transient enhancement of memory re-stabilization (Ratano et al., 2014). Intra-hippocampal injection of the cannabinoid agonist anandamide blocked reconsolidation of contextual fear measured with freezing response in rats when administered following a brief reactivation session and facilitated extinction when administered following a prolonged reactivation session (de Oliveira Alvarenga et al., 2008).

Cannabinoid agonists trigger a variety of CB1 receptor-dependent intracellular signaling mechanisms within the brain, including the activation of the mTOR signaling pathways (Gomez et al., 2011). mTOR pathway activation was involved in cannabinoids-induced memory impairment, as pre-treatment with rapamycin blocked the amnesic-like effects promoted by delta-9-tetrahydrocannabinol (THC) administration and inhibition of anandamide degradation (Puigserver et al., 2009; Busquets-Garcia et al., 2011). Hence it has been suggested that mTOR has a specific role in modulating the effects of cannabinoids (Puigserver et al., 2013).

Here we aimed to compare the separated and combined effects of blocking mTOR signaling and enhancing cannabinoids on the reconsolidation of an emotional memory using inhibitory fear conditioning. We used doses that were found to be effective in recent studies and examined whether WIN55,212-2 and rapamycin have an additive effect on reconsolidation (Ganon-Elazar and Akirav, 2009, 2013; Jobim et al., 2012; Segev and Akirav, 2011). We also examined whether this disruption in fear memory reconsolidation would be effective in enhancing subsequent extinction learning and thus could potentially be useful for reducing expression of fear memory.

2. Experimental procedures

2.1. Subjects

Male Sprague-Dawley rats (60 days old, ~220 g; Harlan, Jerusalem, Israel) were caged together (20 cm × 38 cm × 60 cm; 5 per cage) at 22 ± 2 °C under 12-hour light/dark cycles. Rats were allowed water and laboratory rodent chow ad libitum. The experiments were approved by the University of Haifa Ethics and Animal Care Committee and adequate measures were taken to minimize pain or discomfort.

2.2. Drug treatment

Rapamycin (0.28 ng/side or 10 mg/kg i.p.), WIN55,212-2 (WIN: 5 μg/side or 0.5 mg/kg i.p.), and AM251 (0.3 mg/kg i.p.) were from Cayman Chemicals. Drugs were initially dissolved in DMSO, and further diluted with 1% Tween 80 and 98% saline (0.9% NaCl). Drug doses were based on previous studies (Ganon-Elazar and Akirav, 2009; Jobim et al., 2012; 2013; Segev and Akirav, 2011).

2.3. Surgery and drug microinjection

Described in Ganon-Elazar and Akirav (2009). Briefly, rats were anesthetized with 4.8 ml/kg Equithesin i.p.: 2.12% w/v MgSO4, 10% ethanol, 39.1% v/v propylene glycol, 0.98% w/v sodium pentobarbital and 4.2% w/v chloral hydrate), and implanted with a stainless steal guide cannula aimed above the dorsal CA1 (AP − 4.2 mm; LM ± 2.5 mm; VD − 2.3 mm), BLA (AP − 2.6 mm; LM ± 5.0 mm; VD − 6.8 mm), or the anterior IC (AP +1.1 mm; LM ± 5.5 mm; VD − 6.0 mm). Animals were allowed 1 week to recuperate before the experiment. Microinjection was performed bilaterally in a 0.5-μl volume per side delivered over 1 min. The injection cannula was connected via polyethylene PE20 tubing to a Hamilton microsyringe driven by a microinfusion pump (PHD1000, Harvard Apparatus).

2.4. Light-dark avoidance avoidance

Animals were placed in an inhibitory avoidance apparatus (50 cm × 25 cm × 30 cm), divided into two equal-size compartments, and separated by an automatic guillotine door.

2.4.1. Conditioning

On day 1, each rat was placed in the light compartment and after 2 min of exploration the door was raised allowing access to the dark...
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