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The effects of cannabinoid receptors activation and glucocorticoid receptors deactivation in the amygdala and hippocampus on the consolidation of a traumatic event

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ABSTRACT

Ample evidence demonstrates that fear learning contributes significantly to many anxiety pathologies including post-traumatic stress disorder (PTSD).

The endocannabinoid (eCB) system may offer therapeutic benefits for PTSD and it is a modulator of the hypothalamic pituitary adrenal (HPA) axis. Here we compared the separated and combined effects of blocking glucocorticoid receptors (GRs) using the GR antagonist RU486 and enhancing CB1r signaling using the CB1/2 receptor agonist WIN55,212-2 in the CA1 and basolateral amygdala (BLA) on the consolidation of traumatic memory. Traumatic memory was formed by exposure to a severe footshock in an inhibitory avoidance apparatus followed by exposure to trauma reminders.

Intra-BLA RU486 (10 ng/side) and WIN55,212-2 (5 μg/side) administered immediately after shock exposure dampened the consolidation of the memory about the traumatic event and attenuated the increase in acoustic startle response in rats exposed to shock and reminders. In the CA1, WIN55,212-2 impaired consolidation and attenuated the increase in acoustic startle response whereas RU486 had no effect. The effects of WIN55,212-2 were found to be mediated by CB1 receptors, but not by GRs. Moreover, post-shock systemic WIN55,212-2 (0.5 mg/kg) administration prevented the increase in GRs and CB1 receptor levels in the CA1 and BLA in rats exposed to shock and reminders.

The findings suggest that the BLA is a locus of action of cannabinoids and glucocorticoids in modulating consolidation of traumatic memory in a rat model of PTSD. Also, the findings highlight novel targets for the treatment of emotional disorders and PTSD in particular.

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1. Introduction

Debilitating fear memories, where responses are enhanced and fail to extinguish, may be an important mechanism for the subsequent development of anxiety disorders such as post-traumatic stress disorder (PTSD). PTSD has in fact been associated with enhanced acquisition and slower extinction of fear responses and it has been suggested that exposure to trauma reminders might impair extinction (Orr, Meyerhoff, Edwards, & Pitman, 1998; Orr et al., 2000; Wessa & Flor, 2007).

Recent clinical (Fraser, 2009; Hauer et al., 2013; Roitman, Mechoulam, Cooper-Kazaz, & Shalev, 2014) and preclinical (Ganon-Elazar & Akirav, 2012; Hill & Gorzalka, 2009; Korem & Akirav, 2014; Lutz, Marsicano, Maldonado, & Hillard, 2015; Moreira & Wotjak, 2010) studies pointed the endocannabinoid (eCB) system as a possible therapeutic target to treat both the emotional and cognitive dysfunctions characterizing PTSD (Trezza & Campolongo, 2013). The eCB system includes the cannabinoid receptors (CB1r and CB2r), eCBs (N-arachidonylethanolamine [AEA/anandamide] and 2-arachidonoyl-glycerol [2-AG]), and enzymes involved in their synthesis and metabolism (fatty acid amide hydrolase (FAAH) for AEA and the monoacylglycerol lipase (MAGL) for 2-AG). Several lines of evidence support the role of the eCB system as a modulator of the hypothalamic pituitary adrenal (HPA) axis (Patel, Roelke, Rademacher, Cullinan, & Hillard, 2004; Häring, Guggenhuber, & Lutz, 2012; Akirav, 2013) and of the behavioral responses to stress, including anxiety-related behaviors, and extinction of fear memories (Ganon-Elazar and Akirav, 2012; Steiner et al., 2008).

There is evidence that infusions of cannabinoid agonists systemically, into the hippocampus or into the amygdala impair the consolidation of aversive memory including inhibitory avoidance, contextual fear conditioning and spatial water-maze training

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(Barros et al., 2004; Castellano, Rossi-Arnaud, Cestari, & Costanzi, 2003; Pamplona & Takahashi, 2006; Robinson et al., 2008; Kuhnert, Meyer, & Koch, 2013; Moshfegh, Babaei, Oryan, Soltani, & Zarrindast, 2011; Nasehi, Sahebgharani, Haeri-Rohani, & Zarrindast, 2009; Rezayof, Sardari, Zarrindast, & Nayer-Nouri, 2011; Zarrindast, Ghiasvand, Rezayof, & Ahmadi, 2012). However, there is contrasting evidence that intra-BLA post-training infusions of cannabinoids enhance the consolidation of inhibitory avoidance tested 48 h after conditioning (Atsak et al., 2015; Campolongo et al., 2009; Morena et al., 2014).

Glucocorticoid hormones are essentially involved in strengthening the consolidation of long-term memory of emotionally arousing experiences in animals and humans (Buchanan & Lovallo, 2001; De Kloet, Oitzl, & Joëls, 1999; Joëls, Pu, Wiegert, Oitzl, & Krugers, 2006; Kuhlmann & Wolf, 2006; Roozendaal, 2000; Sandi et al., 2007; De Quervain, Aerni, Schelling, & Roozendaal, 2009; Roozendaal & McGaugh, 2011; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012). Intra-BLA or intra-hippocampal glucocorticoid receptor (GR) antagonists were found to block the effects of stress on memory and plasticity (Maroun & Akirav, 2008; Ramot & Akirav, 2012; Sapolsky, 2003; Segev & Akirav, 2016) and to impair aversive memory such as contextual fear conditioning and spatial learning in a water maze (Cordero, Kruyt, Merino, & Sandi, 2002; Cordero & Sandi, 1998; Donley, Schulkin, & Rosen, 2005; Fleshner, Pugh, Tremblay, & Rudy, 1997; Pugh, Fleshner, & Rudy, 1997; Roozendaal & McGaugh, 1997). Thus, it has been suggested that GRs are critically involved in the formation of aversive/emotional memories.

Blocking GRs and enhancing eCBs were found to prevent the effects of stress on a variety of memory tasks (de Kloet, de Kock, Schild, & Veldhuis, 1988; Ganon-Elazar & Akirav, 2013; Maroun & Akirav, 2008; Oomen, Mayer, de Kloet, Joels, & Lucassen, 2007; Ramot & Akirav, 2012; Roozendaal, Brunson, Holloway, McGaugh, & Baram, 2002; Segev, Ramot, & Akirav, 2012; Segev, Rubin, Abush, Richter-Levin, & Akirav, 2014; Wulsin, Herman, & Solomon, 2010). Moreover, studies indicate a bidirectional relationship between glucocorticoids and the eCB system (for review see: Akirav, 2013; Di, Malcher-Lopes, Halmos, & Tasker, 2003; Tasker & Joëls, 2015; Di et al., 2016; Hillard, Beatka, & Sarvaideo, 2016; Morena, Patel, Bains, & Hill, 2016). ECBs play a key role in regulation of the HPA axis under basal and stressful conditions (Patel et al., 2004; Steiner & Wotjak, 2008; Ganon-Elazar & Akirav, 2009; Hill et al., 2010a; Ganon-Elazar & Akirav, 2012; Ganon-Elazar & Akirav, 2013; Gray et al., 2015; Hill & Tasker, 2012). Stress and glucocorticoids can trigger eCB synthesis and CB1 receptors signaling to constrain HPA axis activity under acute conditions (Hill et al., 2011; Marsicano et al., 2002; Rademacher et al., 2008), whereas chronic corticosterone or chronic unpredictable stress leads to a functional down-regulation in CB1 receptors signaling (Patel & Hillard, 2008).

Here we aimed to compare the separated and combined effects of blocking GRs and enhanced CB1r signaling on the consolidation of a traumatic memory. To that end, rats were microinjected with the CB1/2 receptor agonist WIN55,212-2 or the GR antagonist RU486 into the BLA and CA1 immediately after a traumatic event and tested for fear consolidation, extinction and acoustic startle response a month later. We also examined alterations in CB1r and GRs in the BLA and CA1.

We used a PTSD model in which rats are exposed to a severe footshock in an inhibitory avoidance apparatus followed by contextual situational reminders (SRs) of the shock, and tested one month after shock exposure. Previous studies with this model demonstrated that mice showed increased anxiety-like behaviors, heightened startle reflexes, learned helplessness, and impaired social behavior (Louvart, Maccari, Ducrocq, Thomas, & Darnaudéry, 2005; Pynoos, Ritzmann, Steinberg, Goenjian, & Prisecaru, 1996). We recently found that rats exposed to shock and reminders showed impaired fear extinction, impaired plasticity in the hippocampal-accumbens pathway, and enhanced latency to startle one week after shock exposure (Korem & Akirav, 2014).

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (60 days old, ~300 g; Harlan, Jerusalem, Israel) were caged together (5 per cage) at 22 ± 2 °C under 12-h 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. Pharmacological agents

The CB1/2 receptor agonist WIN55,212-2 (5 μg/side or 0.5 mg/kg i.p.) and the CB1r antagonist AM251 (0.3 ng/side, Cayman Chemicals) were dissolved in 10% dimethylsulfoxide (DMSO), 5% Tween-80, 1% absolute ethanol and saline (0.9% NaCl). Controls were given the vehicle only. The GR antagonist RU486 (10 ng/side; Sigma) was first dissolved in 100% ethanol and subsequently diluted in saline to reach the appropriate concentration. The final concentration of ethanol was 2%. Controls were given the vehicle only. The vehicle used in Fig. 2b, c, f and g contained final concentration of 10% dimethylsulfoxide (DMSO), 5% Tween-80, 2% absolute ethanol and saline (0.9% NaCl). Drug concentrations were based on previous studies (Ganon-Elazar & Akirav, 2012; Ganon-Elazar & Akirav, 2013; Korem & Akirav, 2014; Ramot & Akirav, 2012; Segev et al., 2012(.

2.3. Cannulation and drug microinjection

Rats were anesthetized with 4.8 ml/kg Equithesin (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), restrained in a stereotactic apparatus (Stoelting, Wood Dale, IL), and implanted bilaterally with a stainless steel guide cannula aimed at the BLA or the CA1. The cannulas were positioned in place with acrylic dental cement and secured by two skull screws. A stylus was placed in the guide cannula to prevent clogging. Animals were allowed one week to recuperate before being subjected to experimental manipulations.

For microinjection, the stylus was removed from the guide cannula, and a 28-gauge injection cannula, extending 1.0 mm from the tip of the guide cannula connected via PE20 tubing to a Hamilton micro syringe driven by a microinfusion pump (PHD1000, Harvard Apparatus, USA) was inserted. Microinjection was performed bilaterally in 0.5 μL volume per side delivered over 1 min.

As we previously demonstrated, microinjection of 0.5 μl dye locally into the BLA or CA1 does not spread outside the boundaries of these areas (Abush & Akirav, 2010; Ganon-Elazar & Akirav, 2013). In the current work we have verified the location of the cannula tips histologically so that they all fall within the BLA or the CA1. Rats with misplaced cannulae were excluded from the experiment. While minor diffusion of the drug into neighboring areas cannot be completely excluded, we have demonstrated robust and distinct behavioral results after the microinjection into the CA1 and BLA (Fig. 2b and f).

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