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Cannabinoids and traumatic stress modulation of contextual fear extinction and GR expression in the amygdala-hippocampal-prefrontal circuit

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Summary Considerable evidence suggests that cannabinoids modulate the behavioral and physiological response to stressful events. We have recently shown that activating the cannabinoid system using the CB1/CB2 receptor agonist WIN55,212-2 (WIN) in proximity to exposure to single-prolonged stress (SPS), a rat model of emotional trauma, prevented the stress-induced enhancement of acoustic startle response, the impairment in avoidance extinction and the enhanced negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis (Ganon-Elazar and Akirav, 2012). Some of the effects were found to be mediated by CB1 receptors in the basolateral amygdala (BLA).

Here we examined whether cannabinoid receptor activation in a putative brain circuit that includes the BLA, hippocampus and prefrontal cortex (PFC), could prevent the effects of traumatic stress on contextual fear extinction and alterations in glucocorticoid receptor (GR) protein levels.

We found that: (i) SPS impaired contextual fear extinction tested one week after trauma exposure and that WIN prevented the stress-induced impairment of extinction when microinjected immediately after trauma exposure into the BLA or hippocampus (5 μg), but not when microinjected into the PFC, (ii) the ameliorating effects of WIN on contextual extinction were prevented by blocking GRs in the BLA and hippocampus, and (iii) SPS up regulated GRs in the BLA, PFC and hippocampus and systemic WIN administration (0.5 mg/kg) after trauma exposure normalized GR levels in the BLA and hippocampus, but not in the PFC.

Cannabinoid receptor activation in the aftermath of trauma exposure may regulate the emotional response to the trauma and prevent stress-induced impairment of extinction and GR up regulation through the mediation of CB1 receptors in the BLA and hippocampus. Taken together, the findings suggest that the interaction between the cannabinoid and glucocorticoid systems is crucial in the modulation of emotional trauma.

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1. Introduction

There is increased interest directed at the pharmacological properties of cannabinoids as a possible treatment of stress- and anxiety-related disorders such as post-traumatic stress disorder (PTSD) (Fraser, 2009; Ganon-Elazar and Akirav, 2009; Abush and Akirav, 2010; Akirav, 2011; Ganon-Elazar and Akirav, 2012). The endocannabinoid (eCB) system includes cannabinoid receptors (CB1 and CB2), eCBs (N-arachidonylethanolamine (AEA) and 2-arachidonoyl-glycerol [2-AG]), enzymes involved in their synthesis and metabolism (fatty acid amide hydrolase (FAAH) for AEA and the monoacylglycerol lipase (MAGL) for 2-AG), and an eCB transporter (Devane et al., 1992; Freund et al., 2003; Kogan and Mechoulam, 2006). ECBs act as retrograde messengers and are synthesized on demand post synaptically from lipid precursors.

There is also an increased interest in using glucocorticoids as a treatment for anxiety disorders (Aerni et al., 2004; de Quervain et al., 2011). This is in accordance with the fact that both glucocorticoid receptors (GRs) and CB1 receptors are located within the fear circuitry in the brain (i.e., amygdala, hippocampus and cerebral cortex) (Fuxe and Agnati, 1985; van Eekelen et al., 1987; Ahima and Harlan, 1990; Herkenham et al., 1990; Katona et al., 2001; Korte, 2001; Bentz et al., 2010). This brain circuit has been described as dysfunctional in PTSD as individuals with PTSD typically show exaggerated amygdala and diminished hippocampal activation relative to controls (Shin et al., 2004, 2005). The ventromedial prefrontal cortex (vmPFC) has been mostly reported to be hypoactive in PTSD, but a few have reported hyperactivity (Bryant et al., 2005; Shin et al., 2005).

Impaired extinction of fear memories is thought to contribute to the development and persistence of anxiety disorders including PTSD (e.g., Lissek et al., 2005; Milad et al., 2007). PTSD patients also demonstrate impaired extinction of fear that is not related to the trauma. For example, Milad et al. (2008) have shown deficient extinction recall and Orr et al. (2000) found resistance to extinction following fear conditioning in PTSD patients. Notably, the BLA, hippocampus and vmPFC are part of the neurocircuitry mechanism involved in the extinction of contextual fear (Sotres-Bayon et al., 2004). The infralimbic (IL) and prelimbic (PL) areas (which compose the vmPFC) exert bidirectional control over fear expression, and both likely play a role in extinction retrieval. Specifically, the IL enhances extinction learning (Milad and Quirk, 2002; Milad et al., 2004; Mueller et al., 2008) whereas the PL increases conditioned fear expression (Vidal-Gonzalez et al., 2006).

Activating the eCB system can facilitate fear extinction in different behavioral tasks (Chhatwal et al., 2005; Pamplona et al., 2006; Pamplona et al., 2008; Bitencourt et al., 2008; de Oliveira Alvares et al., 2008; Abush and Akirav, 2010), whereas inhibition of eCB transmission robustly inhibit (or prolong) fear extinction (Marsicano et al., 2002; Suzuki et al., 2004; Pamplona et al., 2006; Ganon-Elazar and Akirav, 2009; Abush and Akirav, 2010). Similarly, studies in animals and humans have shown that glucocorticoids can facilitate extinction processes whereas GR antagonists impair extinction of conditioned fear (Barrett and Gonzalez-Lima, 2004; Yang et al., 2006; Yang et al., 2007; Ninomiya et al., 2010; Blundell et al., 2011; Clay et al., 2011; de Quervain et al., 2011; and see Bitencourt et al., 2013). Human studies suggest that the administration of cortisol can enhance extinction-based psychotherapy (Aerni et al., 2004; de Quervain et al., 2011) and animal studies demonstrate that GR agonists can facilitate the extinction of contextual fear and fear potentiated-startle (Cai et al., 2006; Yang et al., 2006; Ninomiya et al., 2010; Blundell et al., 2011).

We have previously shown that intra-BLA cannabinoid receptor activation using the CB1/2 receptor agonist WIN55,212-2 (WIN) prevented the stress-induced disruption of inhibitory avoidance extinction (Ganon-Elazar and Akirav, 2009). This reversal effect was found to be associated with alterations in the hypothalamic-pituitary-adrenal (HPA) axis, as intra-BLA WIN inhibited the stress-induced increase in plasma corticosterone (CORT) levels. Recently (Ganon-Elazar and Akirav, 2012), we have used the single prolonged stress (SPS) model for PTSD (Liberzon et al., 1997) to demonstrate that cannabinoids administered IP up to 24 h after exposure to traumatic stress (i.e. SPS) prevent the trauma-induced alterations in conditioned avoidance, extinction, acoustic startle response and HPA axis negative feedback. Some of these effects were found to be mediated by CB1 receptors in the BLA (Ganon-Elazar and Akirav, 2012). Nonetheless, the modulation of these stress effects by cannabinoids cannot be explained through only amygdala mediated alterations, in particularly in light of the dense distribution of CB1 receptors in hippocampus and PFC and the involvement of these brain areas in emotional trauma and extinction. Hence, our first aim in this study was to examine the involvement of CB1 receptors in the amygdala, hippocampus and PFC in preventing the effects of exposure to traumatic stress on the extinction of contextual fear.

Many disease states feature HPA axis dysregulation in the form of changes in GR levels, basal CORT secretion, or feedback regulation. Mineralcorticoid receptors (MRs) and GRs are the main receptors for glucocorticoids. Here, we focused on GRs as they are widely expressed in the brain and are occupied during the peak of diurnal CORT secretion as well as by stress levels of CORT whereas MRs are occupied to capacity most of the time (i.e., even during trough levels of glucocorticoids) (Reul and de Kloet, 1985).

We have previously found that one week after SPS trauma exposure rats demonstrate enhanced negative feedback on the HPA axis in response to the dexamethasone test with no apparent effect on baseline CORT levels (Ganon-Elazar and Akirav, 2012). But dexamethasone does not cross the blood brain barrier and acts mostly at the level of the pituitary. Yehuda et al., 2006 reported on a greater ACTH decline in response to hydrocortisone in PTSD patients implying that both peripheral and central GR are more responsive. Importantly, the single dose affected memory performance suggesting that enhanced responsiveness may contribute to PTSD pathophysiology (Yehuda et al., 2007).

Although negative feedback can occur directly within the axis to some degree, structures within the forebrain limbic system (i.e. hippocampus, amygdala and PFC), play an integral role in regulating the system (Herman et al., 2005). Hence, alterations in GRs have a significant influence on HPA axis activity, particularly by modulating the strength of negative feedback and therefore the regulation of glucocorticoid levels (Yehuda et al., 2012). In general, the amygdala activates the HPA axis in response to stressful stimuli whereas the hippocampus and PFC inhibit the HPA axis (for review:

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