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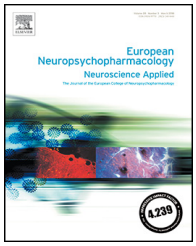

Chronic exposure to cannabinoids before an emotional trauma may have negative effects on emotional function

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Abstract
Chronic direct activation of cannabinoid CB1 receptors (CB1r) may lead to downregulation of CB1r which may in turn result in a depression-like phenotype in certain individuals.
We examined the effects of chronic cannabinoid receptor activation before exposure to an emotional traumatic event on CB1r expression in the basolateral amygdala (BLA) and CA1 and on protracted anxiety- and depression-like behaviors. We used exposure to severe shock and situational reminders (SRs) in an inhibitory apparatus as a model for emotional trauma.
Chronic treatment with the CB1/2 receptor agonist WIN55,212-2 (1.2 mg/kg, i.p.) before shock exposure had differential effects on depression- and anxiety-like behavioral measures depending on withdrawal periods. In the 24 hrs withdrawal condition, WIN55,212-2 enhanced fear retrieval and impaired extinction, increased anhedonia and despair, but had a therapeutic effect in the startle test. In the 10 days withdrawal condition, WIN55,212-2 enhanced fear retrieval and impaired extinction without preventing the shock/SR-induced negative effects on anhedonia or startle response, but had a therapeutic effect in the despair test.
Chronic treatment with WIN55,212-2 was found to down regulate CB1r protein levels in the BLA in the 10 days withdrawal condition, and to upregulate CB1r protein levels in the 24 hrs condition. In the CA1, rats chronically injected with vehicle or WIN55,212-2 demonstrated downregulation of CB1r protein levels.
Chronic exposure to cannabinoids prior to an emotional trauma may have deleterious effects on emotional function suggesting that direct CB1/2 receptor activation may not be an optimal way to manipulate the endocannabinoid system in stressful individuals.

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1. Introduction

The most common self-reported reason for using cannabis is rooted in its ability to reduce feelings of stress. Research has documented elevated rates of cannabis use among individuals with trauma exposure and posttraumatic stress disorder (PTSD). It has been suggested that PTSD patients exhibit a coping-oriented use of cannabis (i.e., self-medication hypothesis) which explains their high prevalence of cannabis use.

Pre-clinical studies suggest that cannabinoids administered acutely after exposure to a traumatic event may prevent or attenuate PTSD-like phenotype (Aisenberg et al., 2017; Korem and Akirav, 2014; Shoshan et al., 2017; Zer-Aviv and Akirav, 2016). Clinical studies suggest that post-trauma treatment with cannabinoids may attenuate PTSD symptoms (Fraser, 2009; Jetly et al., 2015; Roitman et al., 2014).

Chronic exposure to cannabinoid agonists causes a reduction in the number and signaling efficiency of CB1 receptors (CB1r) as a homeostatic response (Breivogel et al., 1999; 2003; McKinney et al., 2008; Sim-Selley et al., 2002) and the downregulation is reversible upon withdrawal (Sim-Selley et al., 2006). Similar findings are present in humans, CB1r binding is decreased in chronic daily cannabis smokers at baseline but recovers to normal levels after withdrawal, and the regional selectivity of downregulation is similar between rodents and humans (Hirvonen et al., 2012).

Due to the increase in the prevalence of cannabis use, we aimed to examine whether chronic exposure to cannabinoids *before* exposure to an emotional traumatic event, would have a therapeutic effect on post-trauma behaviors or might exacerbate the effects of the trauma on behavior. It has been argued (Neumeister et al., 2013) that direct activation of cannabinoid CB1r over an extended period of time may lead to downregulation of CB1r (Hirvonen et al., 2012; Leweke and Koethe, 2008) which may in turn result in a depression-like phenotype in certain individuals (Beyer et al., 2010).

We used the exposure to shock and reminders model of PTSD as the emotional trauma (Shoshan and Akirav, 2017). We have previousely shown that rats exposed to shock and SRs demonstrate enhanced fear retrieval and startle response, impaired extinction, anhedonia, despair and alterations in hippocampal and amygdalar memory processes and plasticity (Aisenberg et al., 2017; Burstein et al., 2018; Shoshan et al., 2017).

We aimed to examine whether chronic administration of the CB1/2 receptor agonist WIN55,212-2 (WIN) before exposure to an emotional traumatic event (with withdrawal periods of 24 hr or 10 days, or with no withdrawal) would attenuate or exacerbate the effects of the trauma on anxiety- and depression-like behaviors measured a month later. A previous study from our lab suggested that 24 hrs after chronic WIN administration there are still substantial residuals of cannabinoids that significantly affect behavior; at 10 days after the last injection there might be some residue of cannabinoids in the brain with less effects on behavior (Abush and Akirav, 2012). In support it has been shown that long-term cannabinoid administration produces CB1r desensitization and down-regulation in the hippocampus that recovers to control level at 14 days after cessation of treatment (Sim-Selley and Martin, 2002).

We also examined the effects of chronic WIN administration on the expression of CB1r in the amygdala and hippocampus, two brain regions that are involved in fear and memory and are highly implicated in PTSD. WIN was selected due to its high affinity to the cannabinoid receptors (Lawston et al., 2000). WIN mimics delta-9-THC (THC), which is also a CB1/2 receptor agonist and it can also mimic most of marijuana and hashish effects (Richardson et al., 2002; Viveros et al., 2005). The exposure to trauma and SRs model allows measuring anxiety, startle response and deficits in fear extinction, defining features of PTSD. Impaired extinction of fear memories is thought to contribute to the development and persistence of anxiety disorders including PTSD (Lissek et al., 2005; Milad et al., 2007). We also measured the effects of shock and SRs on anhedonia, or inability to experience positive emotions, which is a core diagnostic feature of both major depression and PTSD according to DSM-V (APA, 2013) as well as passive coping and behavioral despair (Lucki, 2015).

2. Experimental procedures

2.1. Animals

Male Sprague-Dawley rats (60-day-old, ~250 g; Harlan, Jerusalem, Israel) were caged together at 22 ± 2 °C under 12-h light/dark cycles (lights turned on at 07:00). Rats were allowed water and laboratory rodent chow *ad libitum*. The experiments were approved by the University of Haifa Ethics and Animal Care Committee.

2.2. Drug treatment

The CB1/2 receptor agonist WIN 55,212-2 (1.2 mg/kg, i.p.; one injection per day, injected for 12 days) was dissolved in 1% DMSO, 1% Tween 80 and then diluted with saline (0.9% NaCl) to achieve the final volume. The concentration of DMSO was <1.5% in the final solution. Controls were given vehicle only. WIN concentration was based on studies from our lab and the literature (Abush and Akirav, 2012; Schneider and Koch, 2007; Schneider et al., 2008).

2.3. Exposure to the emotional trauma in the light-dark inhibitory avoidance (IA) apparatus

Rats were placed in an inhibitory avoidance apparatus (for details see: Korem and Akirav, 2014).

Shock (conditioning): Each rat was placed in the light compartment. Thirty seconds after the rat entered the dark compartment, the door closed and the rat received an inescapable 1.5 mA shock for 10 s.

Situational reminders (SRs): Rats were placed in the light compartment for 1 minute with the gate closed in order to prevent them from entering the shock compartment (to avoid extinction).

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