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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A R T I C L E   I N F O

Article history:
Received 2 March 2017
Revised 10 August 2017
Accepted 13 August 2017
Available online 15 August 2017

Keywords:
Post-traumatic stress disorder (PTSD)
WIN55,212-2
Glucocorticoid receptors
CB1 receptors
Extinction, stress

A B S T R A C T

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, Gugenhuber, & 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.
...demonstrated that mice showed increased anxiety-like behaviors, footshock in an inhibitory avoidance apparatus followed by con-...
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