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Review

Cannabinoids and glucocorticoids modulate emotional memory after stress

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ABSTRACT

Bidirectional and functional relationships between glucocorticoids and the endocannabinoid system have been demonstrated. Here, I review the interaction between the endocannabinoid and glucocorticoid/stress systems. Specifically, stress is known to produce rapid changes in endocannabinoid signaling in stress-responsive brain regions. In turn, the endocannabinoid system plays an important role in the downregulation and habituation of hypothalamic–pituitary–adrenocortical (HPA) axis activity in response to stress. Glucocorticoids also recruit the endocannabinoid system to exert rapid negative feedback control of the HPA axis during stress.

It became increasingly clear, however, that cannabinoid CB1 receptors are also abundantly expressed in the basolateral amygdala (BLA) and other limbic regions where they modulate emotional arousal effects on memory. Enhancing cannabinoids signaling using exogenous CB1 receptor agonists prevent the effects of acute stress on emotional memory. I propose a model suggesting that the ameliorating effects of exogenously administered cannabinoids on emotional learning after acute stress are mediated by the decrease in the activity of the HPA axis via GABAergic mechanisms in the amygdala.

Contents

1. Introduction

The endocannabinoid (eCB) system is involved in regulating the stress response and subsequent changes in neuroendocrine function and emotional behavior (Abush and Akirav, 2010, 2013; Akirav, 2011; de Bitencourt et al., 2013; Ganon-Elazar and Akirav, 2009, 2012, 2013; Hill et al., 2009; Lutz, 2009; Marsicano et al., 2002; Patel et al., 2005a,b; Viveros et al., 2005). Some findings indicate that endocannabinoid activity is essential for mediating some of the central effects of glucocorticoids (Barna et al., 2004; Weidenfeld et al., 1994). The first evidence of functional interaction between eCB and glucocorticoid systems came from the study by Di et al. (2003). They found that within minutes after their administration, glucocorticoids facilitate endocannabinoid production and release in specific hypothalamic regions regulating hypothalamic–pituitary–adrenocortical (HPA) axis activity (Di et al., 2003).

The glucocorticoid–eCB systems interact in a variety of physiological processes including memory processes. Aversive learning

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is necessary for an individual to survive, since it helps in the avoidance of potentially dangerous situations. When exposed to such situations, proper regulation of emotional responses is essential for healthy living, since the lost of emotional tuning may contribute to the development of trauma-related diseases, including anxiety and mood disorders (Quirk and Mueller, 2008).

Most cannabinoid effects in the brain occur through activation of CB1 receptors, which are densely expressed in regions known to play an important role in anxiety and aversive learning, such as the amygdala, hippocampus and cerebral cortex (Childers and Breivogel, 1998). Basically, both glucocorticoid receptors (GRs) and cannabinoid CB1 receptors are located within this brain circuitry which is involved in aversive/emotional learning (Ahima and Harlan, 1990; Herkenham et al., 1990; Katona et al., 2001).

In this review I will focus on the interaction between the eCB and glucocorticoid systems. The effects of cannabinoids on the HPA axis will be described as well as stress and glucocorticoids modulation of cannabinoids. I will provide evidence for the cross-talk between the two systems in modulating emotional memory, suggesting that alterations of the eCB tone using exogenous cannabinoids administration might be helpful in reducing the stress response and may be effective in preventing the occurrence of stress-related diseases. Finally, I will propose a model suggesting that administration of cannabinoid agonists in the BLA following a stressful experience can tune-down the stress response and HPA axis activation via GABAergic mechanisms in the amygdala; these effects of cannabinoids on the stress response modulate emotional learning and memory.

2. Stress and the HPA axis

Stress is most readily defined as any stimulus that presents a challenge to homeostasis including any actual or potential disturbance of an individual's environment. The stress response enables the animal to adapt to the changing environment (Joëls and Baram, 2009).

Stressful stimuli induce a cascade of events that culminates in secretion of glucocorticoids from the cortex of the adrenal gland. Readers are referred to thorough reviews on the stress response and the HPA axis (e.g. Borsook et al., 2012; Jacobson and Sapolsky, 1991; Sapolsky et al., 2000).

Briefly, stressful stimuli cause release of corticotropin-releasing factor (CRF) from the paraventricular (PVN) of the hypothalamus. CRF then stimulates production of corticotrophin (ACTH), causing the secretion of glucocorticoids (corticosterone (CORT) in rats, cortisol in humans) from the adrenal cortex, which then distributes through the circulation and acts to regulate energy stores. Among other effects, glucocorticoids promote glucose mobilization and redirect energy stores necessary for rapid, adaptive responses to stress.

The HPA axis is self-regulatory, utilizing its end-product, glucocorticoids, to normalize its own activation, function, and responsiveness through negative feedback mechanisms. Glucocorticoids mediate their effects by binding to two subtypes of intracellular receptors, the mineralocorticoid receptor (MR) and the GRs. These two receptors differ in their affinity and distribution within the CNS (De Kloet et al., 2005).

Many disease states feature HPA axis dysregulation in the form of changes in GRs levels, basal CORT secretion, or feedback regulation. Structures within the forebrain limbic system (i.e. hippocampus, amygdala and prefrontal cortex (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: Jankord and Herman, 2008).

3. The endocannabinoid system and stress

The early discovery of Δ-9-THC (THC) led to the subsequent identification of the endogenous endocannabinoid system. This system includes the cannabinoid receptors (CB1 and CB2), the endocannabinoids (N-arachidonylethanolamine (anandamide; AEA) and 2-arachidonoyl-glycerol (2-AG)), the enzymes involved in their synthesis and metabolism (fatty acid amide hydrolase (FAAH) for anandamide and the monoacylglycerol lipase (MAGL) for 2-AG), and an endocannabinoid transporter (Kogan and Mechoulam, 2006; Devane et al., 1992). Anandamide, 2-AG, FAAH, and the CB1 receptor are expressed in brain areas involved in stress, fear, emotions, and reward including the amygdala, nucleus accumbens (NAc), hippocampus, and PFC (Breivogel and Sim-Selley, 2009; Herkenham et al., 1991; Pazos et al., 2005).

Studies of the eCB system support its importance for multiple aspects of brain function including modulation of the HPA axis, regulation of mood, anxiety, reward, and extinction of fear learning (Abush and Akirav, 2013; Ganon-Elazar and Akirav, 2009, 2012, 2013; Fattore et al., 2008; Marsicano et al., 2002; Viveros et al., 2005). The involvement of the eCB system in mood and anxiety provides new targets for the development of novel therapeutic agents for a wide range of psychiatric disorders (Abush and Akirav, 2013; Ganon-Elazar and Akirav, 2012; Gorzalka et al., 2008; Viveros et al., 2005).

In support, clinical data show that people suffering from post-traumatic stress disorder (PTSD) may use cannabis to cope with their symptoms (Passie et al., 2012) supporting the self-medication hypothesis explanation for cannabis use. Several studies reported a strong correlation between PTSD symptom severity and the amount of cannabis use (Cougle et al., 2011; Potter et al., 2011). Moreover, the starting point of using cannabis correlated with the onset of PTSD symptoms (Cougle et al., 2011) suggesting that cannabis use was used to help reduce aversive mood states.

Two open label clinical trials demonstrated potential benefits of cannabis in patients with PTSD. Fraser (2009) found that the synthetic cannabinoid nabilone significantly improved treatment-resistant nightmares in PTSD patients. Subjective improvement in sleep time, the quality of sleep, and the reduction of daytime flashbacks and night sweats were also noted by some patients. Recently, Shalev's group (Roitman et al., 2013) reported that 10 outpatients with chronic PTSD that received THC twice a day for 3 weeks demonstrated a significant improvement in arousal, sleep quality and nightmares.

4. Glucocorticoid and endocannabinoid cross-talk

Experimental studies indicate a bidirectional, functional relationship between glucocorticoids and the eCB system. ECBs play a key role in regulation of the HPA axis under basal and stressful conditions (Ganon-Elazar and Akirav, 2009, 2012, 2013; Patel et al., 2004). 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 CORT or chronic unpredictable stress leads to a functional down-regulation in CB1 receptors signaling (Patel and Hillard, 2008).