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Review

The endocannabinoid system: An emotional buffer in the modulation of memory function

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ABSTRACT

Extensive evidence indicates that endocannabinoids modulate cognitive processes in animal models and human subjects. However, the results of endocannabinoid system manipulations on cognition have been contradictory. As for anxiety behavior, a duality has indeed emerged with regard to cannabinoid effects on memory for emotional experiences. Here we summarize findings describing cannabinoid effects on memory acquisition, consolidation, retrieval and extinction. Additionally, we review findings showing how the endocannabinoid system modulates memory function differentially, depending on the level of stress and arousal associated with the experimental context. Based on the evidence reviewed here, we propose that the endocannabinoid system is an emotional buffer that moderates the effects of environmental context and stress on cognitive processes.

1. Introduction

Emerging evidence indicates that cannabinoid drugs can induce distinct and often opposite effects on anxiety, cognition, and several other behaviors, depending on stress level and the aversiveness of the context (Campolongo et al., 2012; Haller et al., 2009; Szuster, Pontius, & Campos, 1988; Zanettini et al., 2011). Although cannabinoid signaling has been demonstrated to influence memory processing (Campolongo, Roozendaal, Trezza, Hauer, et al., 2009; Marsicano et al., 2002), it is difficult to define its exact role because, regardless of the pharmacodynamic properties of the drug, both impairing and enhancing effects have been reported with cannabinoid drug administration. Although such discrepancies are not unusual in memory research, the factors contributing to these conflicting findings remain poorly understood.

In this review, we begin with a summary of the differing memory modulatory effects of endocannabinoids reported in the literature. We then discuss in detail the biphasic/opposite effects induced by cannabinoid drugs, including evidence that such effects may be strongly dependent on the aversiveness of environmental context and on the level of stress at the time of drug administration and/or training. Finally, with the ultimate aim of developing an explanation of the apparent discrepancies among studies of cannabinoid effects on memory function, we propose hypotheses to explain the observed dual/opposing effects of cannabinoids on emotional memory functions.

2. The endocannabinoid system

The discovery of the main psychoactive constituent of marijuana, Δ^9-tetrahydrocannabinol (Δ^9-THC), led to the identification of the endogenous endocannabinoid system (Gaoni & Mechoulam, 1964). The endocannabinoid system is a lipid signaling system in the brain that begins to exhibit functional activity early in brain development by way of modulating neurotransmitter release, pre- and post-natally (Campolongo, Trezza, Palmery, Trabace, & Cuomo, 2009; Campolongo, Trezza, Ratano, Palmery, & Cuomo, 2011; Fernandez-Ruiz, Berrendero, Hernandez, & Ramos, 2000; Fride, 2004; Harkany et al., 2007; Trezza et al., 2008, 2012). Although many molecular targets of the endocannabinoid system have been described, the primary targets of cannabinoid compounds are the type 1 and type 2 cannabinoid receptors (CB1 and CB2, respectively) (Devane, Dysarz, Johnson, Melvin, & Howlett, 1988; Herkenham et al., 1990; Matsuda, Lolait, Brownstein, Young, & Bonner, 1990).

The two major endogenous ligands for the CB1 and CB2 receptors are *N*-arachidonoyl ethanolamine (anandamide, AEA) (Devane et al., 1992) and 2-arachidonoyl glycerol (2-AG) (Sugiura et al., 1995). AEA acts as a partial agonist of CB1 and CB2 receptors (Pertwee, 2010), whereas 2-AG is full agonist of these receptors (Stella, Schweitzer, & Piomelli, 1997). Unlike classical neurotransmitters,

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endocannabinoids are not stored in presynaptic vesicles, but rather are synthesized postsynaptically from lipid membrane precursor molecules in an activity-dependent manner (Kano, Ohno-Shosaku, Hashimotodani, Uchigashima, & Watanabe, 2009). Once released from the postsynaptic membrane into the synaptic cleft, they travel backward to bind cannabinoid receptors expressed on presynaptic terminals. Activation of CB1 receptors inhibits neurotransmitter release by modulating several ion channels and kinases (Kano et al., 2009; Turu & Hunyady, 2010). Following receptor activation, AEA and 2-AG are deactivated by a still poorly defined uptake process involving a transporter mechanism (Fu et al., 2011; Hillard, Edgemond, Jarrahian, & Campbell, 1997). Subsequently, they are metabolized mainly by their respective degradative enzymes, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) (Kano et al., 2009).

CB1 receptors represent the most abundant class of G-protein-coupled receptors in the central nervous system, and are also present in a variety of peripheral tissues. They couple with both G_i and G_o proteins, which inhibit adenylyl cyclase activity, activate potassium channels, and inhibit voltage-gated calcium channels (Howlett et al., 2002). CB1 receptors are expressed abundantly in major structures of the limbic system, including the hippocampus and basolateral complex of the amygdala (BLA), as well as in the prefrontal cortex (PFC), which is closely linked with limbic structures (McPartland, Glass, & Pertwee, 2007); low levels of CB1 mRNA have also been detected in the central nucleus of the amygdala (CeA) (Kamprath et al., 2010; Marsicano & Lutz, 1999; Matsuda, Bonner, & Lolait, 1993). Within these limbic regions, the CB1 receptor is expressed at very high levels in cholecystokinin-positive GABAergic interneurons (Azad et al., 2008; Marsicano & Lutz, 1999; Morozov, Torii, & Rakic, 2009) and at moderate levels in glutamatergic terminals (Kano et al., 2009; Kawamura et al., 2006; Monory et al., 2006). The CB1 receptor has also been detected on serotonergic, noradrenergic, and dopaminergic terminals (Haring, Marsicano, Lutz, & Monory, 2007; Hermann, Marsicano, & Lutz, 2002; Oropeza, Mackie, & Van Bockstaele, 2007).

The CB2 receptor is a $G_{i/o}$ protein-coupled receptor (Howlett et al., 2002). CB2 receptors are located mostly in the periphery on immunological tissues. They were confirmed only recently by immunohistochemical analyses to be expressed by neurons and glia in diverse rat brain areas, including the cerebellum and hippocampus (Onaivi et al., 2006; Van Sickle et al., 2005).

Studies examining the functions of endocannabinoid signaling in the limbic system have shown that CB1 receptors play a key role in modulating synaptic transmission (Katona et al., 2001; Tan et al., 2011) and neuronal firing (Pistis et al., 2004). Furthermore, growing evidence indicates that endocannabinoids play a key role in modulating emotional memory processes (Atsak, Roozendaal, & Campolongo, 2012; Campolongo, Roozendaal, Trezza, Hauer, et al., 2009; Ganon-Elazar & Akirav, 2009; Marsicano & Lafenetre, 2009; Marsicano et al., 2002; Tan et al., 2011; Wotjak, 2005). In the succeeding sections, we provide a review of findings from studies that examined cannabinoid effects on emotional memory function, focusing especially on the functional relationship between endocannabinoids and glucocorticoids in modulating cognitive processes. Subsequently, we discuss how stress and arousal state may modulate endocannabinoid effects on memory.

3. Modulation of memory for emotional experiences

Emotional learning is extremely important for the survival of an individual; indeed life events of positive and negative valence typically leave lasting and vivid memories due to arousal and stress hormone effects on memory consolidation (McGaugh, 2000). Emotionality describes a highly complex repertoire of behaviors triggered by various environmental stimuli. The regulation of emotional responses under different environmental conditions is essential for mental health and requires fine-tuned neurotransmitter release processes as well as functional neuronal circuits (Gold, 2004; McEwen, 2012; McGaugh, 2000). During emotionally arousing situations, stress hormones are released from the adrenal medulla (epinephrine) and cortex (corticosterone [CORT] in rats, cortisol in humans) into the bloodstream. These systemic stress hormones stimulate the vagus nerve in the periphery, thereby activating the nucleus of tractus solitarius (NTS) in the brainstem, which releases memory modulatory norepinephrine into limbic brain structures (McGaugh & Roozendaal, 2002).

Additionally, glucocorticoid hormones, which are highly lipophilic, readily enter the brain where they bind mineralocorticoid receptors (MRs) with high affinity and glucocorticoid receptors (GRs) with low affinity. Thus, under basal conditions, only MRs are occupied, but during and immediately after a stressful experience, both MRs and GRs are bound by glucocorticoids (Reul & de Kloet, 1985). Extensive evidence indicates that stress hormones, in concert with several other stress-activated systems, mediate the selective enhancement of consolidation of memory for emotionally significant experiences (de Kloet, Oitzl, & Joels, 1999; Joels & Baram, 2009; Oitzl & de Kloet, 1992; Roozendaal, 2000; Sandi & Rose, 1994). Conversely, glucocorticoids typically impair memory retrieval and working memory during emotionally arousing test situations (de Quervain, Aerni, Schelling, & Roozendaal, 2009; de Quervain, Roozendaal, & McGaugh, 1998; Roozendaal, 2000; Roozendaal, de Quervain, Schelling, & McGaugh, 2004).

The neural circuitry underlying emotionality is considerably complex, but broadly consists of subcortical limbic structures, such as the amygdala, hippocampus, ventral striatum, and thalamus, as well as cortical structures, including the anterior cingulate cortex and medial and orbital regions of the PFC (Price & Drevets, 2010). This corticolimbic circuit interacts with visceral autonomic centers in the hypothalamus and brain stem to regulate emotional expression and to modulate the activity of the hypothalamic–pituitary–adrenal (HPA) axis (Price & Drevets, 2010). In this assembly, the amygdala represents a key region for the association of environmental information with emotional significance. Although the acquisition of emotional salience by external stimuli has been studied most extensively in relation to fear and anxiety responses, the amygdala has also been shown to be important for the processing of positive emotions, such as in stimulus-reward learning (Aggleton, 1993; Baxter & Murray, 2002; Davis, Rainnie, & Cassell, 1994; Pape & Pare, 2010).

In particular, considerable evidence indicates not only that stressors increase neuronal activity in the BLA (Pelletier, Likhtik, Filali, & Pare, 2005), but also that emotional memory modulation requires activation of the BLA specifically. For example, lesions of the BLA, but not the CeA, block the memory enhancing effects of systemic GR activation on inhibitory avoidance retention (Roozendaal & McGaugh, 1996). Furthermore, posttraining infusion of norepinephrine or a β-adrenoceptor agonist into the BLA enhances memory of training on several learning tasks (Ferry & McGaugh, 1999; Hatfield, Spanis, & McGaugh, 1999; LaLumiere, Buen, & McGaugh, 2003; Roozendaal, Castello, Vedana, Barsegyan, & McGaugh, 2008). In contrast, attenuation of noradrenergic signaling by infusion of a β-adrenoceptor antagonist (propranolol or atenolol) into the BLA, but not into the neighboring CeA, has been shown to block the memory enhancement induced by systemic or intra-BLA administration of a GR agonist (Quirarte, Roozendaal, & McGaugh, 1997; Roozendaal, Quirarte, & McGaugh, 2002). Considerable evidence developed in rodent studies indicates that glucocorticoid-induced enhancement of memory consolidation depends upon an interaction with noradrenergic activation within the BLA (Roozendaal, McEwen, & Chattarji, 2009). Importantly, a