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Involvement of medial prefrontal cortex alpha-2 adrenoceptors on memory acquisition deficit induced by arachidonylcyclopropylamide, a cannabinoid CB_1 receptor agonist, in rats; possible involvement of Ca^{2+} channels

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Abstract

Functional interactions between cannabinoid and alpha-2 adrenergic systems in cognitive control in the medial prefrontal cortex (mPFC) seem possible. The present study evaluated the possible role of alpha-2 adrenoceptors of the prefrontal cortex on effect of arachidonylcyclopropylamide (ACPA), a cannabinoid CB_1 receptor (CB_1R) agonist, in adult male Wistar rats. The animals were bilaterally implanted with chronic cannulae in the mPFC, trained in a step-through task, and tested 24 h after training to measure step-through latency. Results indicate that pre-training microinjection of ACPA (0.05 and 0.5 µg/rat) and clonidine (alpha-2 adrenoceptor agonist; 1 and 2 µg/rat) reduce memory acquisition. Pre-training subthreshold dose of clonidine (0.5 µg/rat) restored memory-impairing effect of ACPA (0.05 and 0.5 µg/rat). On the other hand, pre-training administration of the alpha-2 adrenoceptor antagonist yohimbine in all doses used (0.5, 1, and 2 µg/rat) did not affect memory acquisition by itself, while a subthreshold dose of yohimbine (2 µg/rat) potentiated memory impairment induced by ACPA (0.005 µg/rat). Finally, a subthreshold dose of SKF96365 (a Ca^{2+} channel blocker) blocked clonidine and yohimbine effect of memory responses induced by ACPA. In conclusion, these data indicate that mPFC alpha-2 adrenoceptors play an important role in ACPA-induced amnesia and Ca^{2+} channels have a critical role this phenomenon.

Keywords

Clonidine, yohimbine, arachidonylcyclopropylamide, inhibitory avoidance memory, medial prefrontal cortex

Introduction

Marijuana and other derivatives of the plant *Cannabis sativa* have psychotropic actions such as euphoria, appetite stimulation, sedation, altered perception, and impairments of memory and motor control (Adams and Martin, 1996). The best-known effects of cannabis consumption are associated with executive functioning and retrospective memory (Solowij and Battisti, 2008). In the brain, cannabinoid CB_1 receptor (CB_1R) and CB_2 receptor (CB_2R), which are G-protein-coupled receptors (GPCRs), mediate the effects of psychoactive principle of cannabis (Δ^9-tetrahydrocannabinol) and synthetic cannabinoids. The CB_2 receptor is expressed in the immune system, with far lower concentrations in the brain (Howlett et al., 2002), while CB_1R are highly expressed in such brain structures as the hippocampus and medial prefrontal cortex (mPFC) classically involved in learning and memory (Glass et al., 1997). The mPFC contains the cannabinoid receptors as well as the endogenous cannabinoid compounds (Bisogno et al., 1999; Di Marzo et al., 2000; Tsou et al., 1998). Despite numerous studies on the effects of the cannabinoid system in learning and memory, there have been conflicting results (Puighermanal et al., 2013; Terranova et al., 1995). In addition, the effects of the cannabinoid system on synaptic plasticity and

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long-term potentiation (LTP) remain controversial (Collins et al., 1994; Misner and Sullivan, 1999; Terranova et al., 1995). According to some of these studies, cannabinoid receptor agonist impair memory formation (Hampson et al., 1999; Hoffman et al., 2007; Lichtman et al., 1995), while other studies indicated that the endocannabinoid system promotes memory function (Marsicano et al., 2002; Niyuhire et al., 2007; Suzuki et al., 2004). The discrepancy between studies may be due to the emotional nature of the behavioral tasks employed and probably reflects the effects of cannabinoids on different brain areas involved in distinct types of memories, acute or chronic exposure to cannabinoid drugs, and doses of these drugs. Given the established role of CB_1R in the acquisition, encoding, and retrieval of memories (Riedel and Davies, 2005), variations in this receptor population possibly mediate the detected effects of cannabis use on memory (Castillo et al., 2012; Montgomery and Fisk, 2007). The cannabinoid system interacts with several neurotransmitter systems (Coulston et al., 2011) such as acetylcholine, dopamine, serotonin, gamma-aminobutyric acid (GABA), glutamate, and noradrenaline by activation of CB_1R (Al-Hayani and Davies, 2002; Schlicker and Kathmann, 2001).

It has been shown that noradrenaline and adrenergic receptors are involved in learning and memory (Hatfield and McGaugh, 1999). Consistent with this, alpha-2 adrenoceptors play critical role in spatial working memory (Arnsten and Goldman-Rakic, 1985; Arnsten et al., 1988; Cai et al., 1993; Ji et al., 2008; Jin et al., 2007). According to previous studies, a noradrenergic mechanism, at least in part, modulates inhibitory avoidance memory (Cecchi et al., 2002; Davis et al., 1994; Ferry et al., 1997; Liang et al., 1986).

It has also been reported that alpha-2 noradrenergic receptor agonists selectively reverse memory impairment in aged monkeys and rats, Conversely, noradrenergic antagonists reduce delay-dependent neuronal activity in the monkey mPFC. For instance, when noradrenergic antagonists are injected locally in the mPFC, they impair working memory performance (Rossetti and Carboni, 2005). Two main classes of receptors, alpha and beta both coupled with G-proteins mediate noradrenaline signals (Piri and Zarrindast, 2011). According to differences in ligand specificity, kinetics, and effects, alpha adrenergic receptors are divided into two subtypes (alpha-1 and alpha-2) (Piri and Zarrindast, 2011; Ranganathan and D'Souza, 2006). Alpha-2 subtypes are expressed in the mPFC. Beneficial effects of noradrenaline on memory functions of mPFC are mediated via alpha-2 adrenoceptors stimulation (Franowicz et al., 2002). although both pre- and post-synaptically have been localized, these receptors have a post-synaptic site of action in the mPFC as several studies have indicated (Levy, 2008). In rats, it has been shown that alpha-2 agonists such as clonidine attenuate memory impairments caused by phencyclidine (PCP) (Jentsch and Anzivino, 2004; McCann et al., 1987; Marrs et al., 2005). Given the beneficial effects of clonidine and related alpha-2 agonists on prefrontal cortical function (Li et al., 1999; Wang et al., 2007) as well as the important role of the prefrontal cortex in the positive actions of alpha-2 agonists on memory function (Arnsten and Goldman-Rakic, 1985), it is likely that if clonidine improves memory, this phenomenon would be linked to enhanced prefrontal cortical function. The increased tonus of neurotransmission in the prefrontal cortex provided by drugs, such as clonidine, could conceivably enable this brain region to effectively process memory demands normally handled by hippocampal neurons.

Brain monoamines are involved in cannabinoid-induced behaviors (Fišar, 2012). Based on neuroanatomical studies, CB_1 receptors localized presynaptically to the cortical noradrenergic axon terminals modulate release of cortical norepinephrine. It seems that noradrenergic efferents of the locus coeruleus (LC) to the frontal cortex regulate attention and cognitive processing. On the other hand, cannabis consumption disrupts the ability to attentively focus attention and reject irrelevant information, suggesting that impact of cannabinoids on the noradrenergic coeruleo-cortical pathway may cause changes in attention, cognition and anxiety as this circuit is involved in modulating these behaviors (Cathel et al., 2014). These findings provide evidence for a functional interaction between cannabinoid and alpha-2 adrenergic receptors. Piri et al. reported that intra-CA_1 administration of clonidine reverses cannabinoid-induced amnesia while yohimbine inhibits cannabinoid state-dependent learning (Piri and Zarrindast, 2011).

Despite the functional cross talk between these two systems, relatively few investigations concentrated on the overlap of cannabinoids and norepinephrine in memory process. Since the interaction between mPFC alpha-2 adrenergic and CB_1Rs in memory process has not been shown previously, the present study was designed to evaluate the effects of mPFC alpha-2 adrenergic receptor on arachidonylcyclopropylamide (ACPA)-induced inhibitory avoidance (IA) memory deficits. Moreover, given the involvement of Ca^{2+} on synaptic transmission of alpha-2 adrenergic (Lechner et al., 2005; Timmons et al., 2004) the role of Ca^{2+} in the above-mentioned processes was assessed using a Ca^{2+} channel blocker, SKF96365.

Material and methods

Animals

Adult male Wistar rats 2.5 months old (Pasteur Institute, Tehran, Iran) and weighing 250–300 g at the beginning of the study were used. Animals were housed four per cage with free access to food and water. They were kept in a temperature-controlled (22±2°C) and 12-hour light/12-hour dark cycle (lights on at 07:00). All experiments were carried out during the light phase between 09:00–15:00.). Experimental groups consisted of eight animals and each animal was tested once. In this study the power analysis was selected in 80%, reducing beta to 0.2 ($Z\beta$= 1.282 and $Z\alpha$= 1.645). All procedures were approved by the committee of Ethics of Tehran University of Medical Sciences (Tehran, Iran) and carried out in accordance with the guidelines for care and Use of Laboratory Animals (National Institutes of Health Publication No. 85–23, revised 2010). The total number of animals were used in this study was 192.

Stereotaxic surgery procedures and microinfusion procedures

Animals were intraperitoneally anesthetized with a mixture of ketamine hydrochloride 10% (50 mg/kg) plus xylazine 2% (5 mg/kg) and then placed in a flat-skull position (incisor bar −3.3 mm) relative to the interaural line within a stereotaxic frame. A midline incision was made in the skin and underlying periosteum retracted. Stereotaxic coordinates for medial prefrontal cortex was anterior-posterior: +3.2 mm from bregma, mediolateral: ±0.8 mm from midline and dorsoventral: –2.5 mm from the skull surface (Paxinos

and Franklin, 2004). Two 22-gauge guide-cannulae were implanted bilaterally 1 mm above the prelimbic region of the mPFC. The cannulae were anchored to the skull using dental acrylic. All animals were allowed one week to recover from surgery and clear the anesthetic effects. For drug infusion, animals were manually restrained; the stylets were removed from the guide cannulae and replaced with 27-gauge injection cannulae. Each injection needle was connected to a 2 μL Hamilton syringe by polyethylene tubing (PE-20), 1 mm below the tip of the guide cannulae . The injection solutions were administered in the right and left mPFC area with the total volume of 0.6 μL/rat (0.3 μL/site) over a 60 s period. The injection needles were left in place for an additional 60 s to facilitate diffusion of the drugs. The infusion time and selected drug doses used in the experiments were chosen according to the pilot and published work in scientific literature (Ahmadi et al., 2013; Jamali-Raeufy et al., 2011; Mohammadi et al., 2015; Torkaman-Boutorabi et al., 2015).

Drugs

Drugs used in the present study were: ketamine and xylazine (Alfasan Chemical Co, Woerden, Holland) for animal anesthesia. Other drugs which were purchased from Tocris, Bristol, UK were: ACPA (a potent and selective CB_1R agonist at 0.5, 0.05, 0.005 μg/rat), clonidine hydrochloride (alpha-2 adrenergic receptor agonist, at 0.5, 1, 2 μg/rat), yohimbine (alpha-2 adrenergic receptor antagonist at 0.5, 1, 2 μg/rat) and SKF96365 (a Ca^{2+} channel blocker at 0.01 μg/rat). All drugs were dissolved in 0.9% sterile saline, except for ACPA, which was supplied pre-dissolved in anhydrous ethanol 5 mg/mL (Tocris Cookson Ltd, UK) and was diluted in saline 0.9% to the proper concentration; the vehicle contained a sufficient part of ethanol (final concentration in the injection below 1%) to make the effects of the drugs. All drugs were injected bilaterally into the mPFC area.

IA task

The IA task is a behavioral test to evaluate aversive memory processes. In this test, subjects learn to avoid an environment in which an aversive stimulus was delivered (Gold, 1986; Nasehi et al., 2009).

Step-through apparatus. The step-through inhibitory avoidance apparatus consisted of two compartments: a light box and a dark box. The light box (20×30×20 cm^3) is made of transparent vinyl chloride plates and was illuminated by a 40 W lamp; the dark box (20×30×20 cm^3) is made of black vinyl chloride plates. A sliding guillotine door was placed between the two compartments. Stainless steel grids on the dark compartment floor were electrically connected to a shock generator that produced foot shock (Borj Sanat Co., Tehran, Iran) (Hosseini et al., 2013; Rasekhi et al., 2014).

Measurement of memory

Habituation. In the habituation session the rat was placed in the lighted compartment, facing away from the dark compartment and allowed to explore. After 15 s the guillotine door was fully opened and the rat was allowed to cross to the dark compartment. The latency to cross into the dark room was recorded. When the rat entered the dark compartment with all four paws, the manually guillotine door was closed, and the rat was immediately removed and returned to the home cage. Animals that waited for more than 100 s to enter to the dark compartment were eliminated.

Training. A one-trial step-through inhibitory avoidance task was used. After 30 min, in the training session, the animal was placed in the lighted compartment, then after 15 s the guillotine door was lifted. When the rat entered the dark compartment with all four paws, the guillotine door was closed and a foot shock (50 Hz, 1 mA, 3 s) was immediately delivered. After 20 s, the rat was removed to its home cage. All drugs were injected pre-training.

Testing. On test day (24 h after training), the rat was placed in the light compartment, facing away from the dark compartment. After 15 s, the guillotine door was opened and the latency to enter the dark compartment was recorded (from the time the door is lifted). The rat was removed from the test and returned to the home cage. The step-through latency was taken as a measure of inhibitory avoidance memory. An upper cutoff time of 300 s was set. The retention test was also carried out between 09:00 and 15:00.

Measurement of locomotor activity

To evaluate whether the observed results of drug administration were purely mnemonic or were affected by possible changes in the animal locomotion (e.g. due to the influence of anxiety during the test session), locomotor activity was also investigated immediately after the test session. The locomotion apparatus consisted of a transparent Perspex box (30×30×40 cm^3) with a black Perspex panel (30×30 cm^2 and 2.2 cm thick). The arena floor of apparatus divided into 16 equal-sized squares. Locomotion was recorded based on the number of crossings from one square to another by 16 installed photocells during 5 min (Khakpai et al., 2012).

Statistical analysis

Given the normality of distribution and homogeneity of variance, the results were statistically evaluated using the analysis of variance (ANOVA; one-or two-way), in which mean± standard error of the mean (SEM) of step-through latencies of the experimental groups on the test day were compared. One-way ANOVA was employed for analyzing individual effects of pre-training intra-mPFC administration of ACPA, clonidine, and yohimbine. Interactions between the drugs were analyzed with the two-way ANOVA. Where p-value was significant, further analyses for paired-group comparisons were carried out using post-hoc Tukey's test. In all comparisons $p<0.05$ was used as the criterion for statistical significance.

Verification of cannulae placements

After the testing sessions, each rat was anesthetized with an overdose of chloroform and then 0.6 μL of a 1% methylene-blue solution was bilaterally infused into the mPFC (0.3 μL/side), as described in the drug section. Animals were subsequently decapitated, their brains dissected and post fixated in a 10% formalin solution. After several days, the brains were sliced and injection sites were verified according to Paxinos and Franklin (Paxinos and Franklin, 2004) (Figure 1).

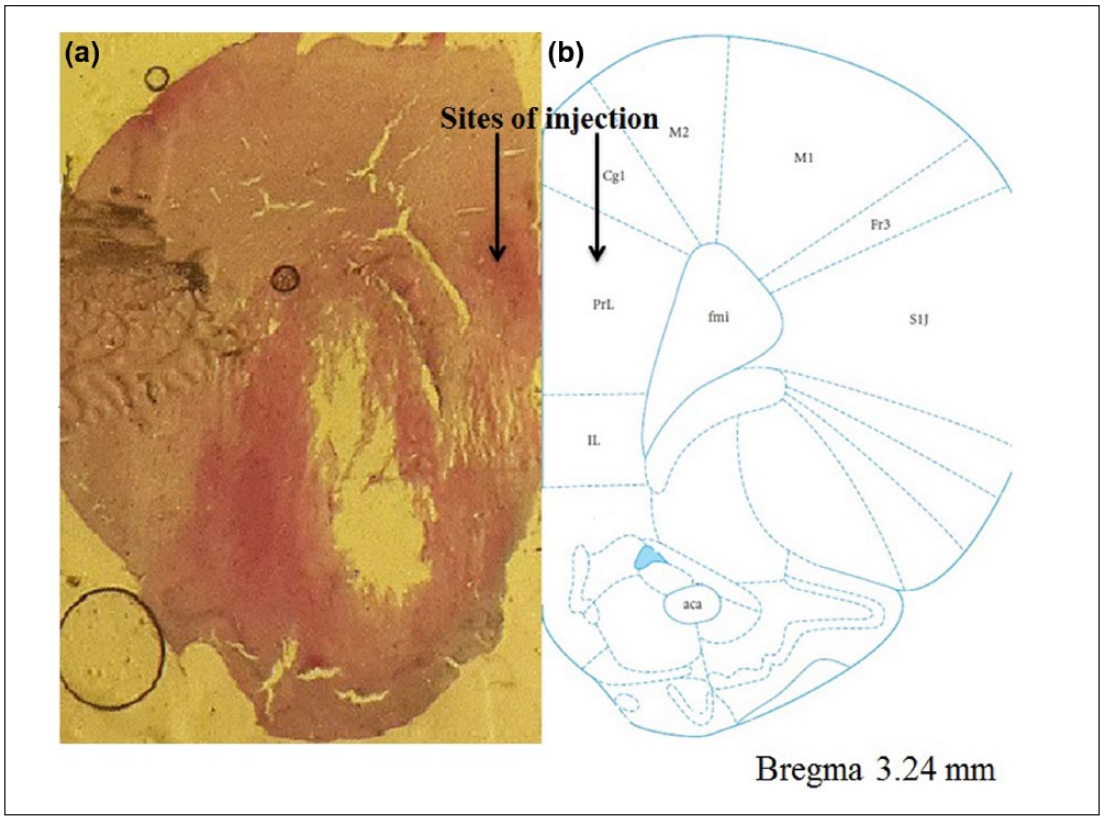

Figure 1. (a) Location of the injection cannula tips in the medial prefrontal cortex (mPFC) of the brain for all rats included in the data analyses. (b) Schematic illustrations of the injection cannula in mPFC are adapted from the atlas of Paxinos and Franklin (2004) *The Mouse Brain in Stereotaxic Coordinates*, with permission from Elsevier.

Experimental design

Eight animals were used in each experimental and control group. Each animal was used only once. The drugs were injected pre-training into the mPFC.

Experiment1. The effect of pre-training intra-mPFC microinjection of clonidine (alpha-2 adrenoceptor agonist) and yohimbine (alpha-2 adrenoceptor antagonist) on IA memory acquisition was examined using eight groups (n=8/group). Four groups were received either saline (0.6 µL/rat) or doses of clonidine (0.5, 1, and 2 µg/rat). The other four groups were received saline (0.6 µL/rat) or yohimbine at doses of 0.5, 1, and 2 µg/rat, 5 min pre-training.

Experiment 2. This experiment evaluated the effect of intra-mPFC administration of ACPA in the absence and presence of subthreshold doses of clonidine or yohimbine on inhibitory avoidance memory. Three four-group sets of animals were used and received pre-training injections of saline (0.6 µL/rat), clonidine (0.5 µg/rat) or yohimbine (2 µg/rat) plus either vehicle (0.6 µL/rat) or ACPA at different doses (0.005, 0.05, and 0.5 µg/rat). The time interval between the injections was 5 min. Step-through latency was measured 24 h after ACPA injections.

Experiment 3. To examine the possible involvement of the mPFC Ca^{2+} channel in responses induced by clonidine and yohimbine on ACPA, four groups of animals were used. Two groups received saline (0.6 µL/rat) and subthreshold dose of SKF96365 (0.01 µg/rat). The other two groups received a subthreshold dose of SKF96365, 5 min before co-administration of clonidine (0.5 µg/rat) plus ACPA (0.5 µg/rat.) or yohimbine (2 µg/rat) plus ACPA (0.005 µg/rat.).

The step-through latency was recorded 24 h later, on the test day. All injections were given before training. Time interval between the injections was 5 min.

Results

Effect of pre-training administration of clonidine and yohimbine on inhibitory avoidance memory

Results of the one-way ANOVA showed that pre-training intra-mPFC administration of clonidine (F(3,28)=20.821, p<0.001) but not yohimbine (F(3,28)=2.108, p>0.05) alter inhibitory avoidance memory acquisition. Post-hoc analyses revealed that clonidine at the doses of 1 and 2 µg/rat impairs inhibitory avoidance memory acquisition (Figure 1(a)). Furthermore clonidine (F(3,28)=2.923, p>0.05) and yohimbine (F(3,28)=2.621, p>0.05) have no effects on locomotor activity (Figure 2).

One-way ANOVA indicated pre-training intra-mPFC administration of ACPA alters inhibitory avoidance memory acquisition (F(3,28)=52.859, p<0.001). Post-hoc analyses showed that ACPA at the doses of 0.05 and 0.5 µg/rat impairs inhibitory

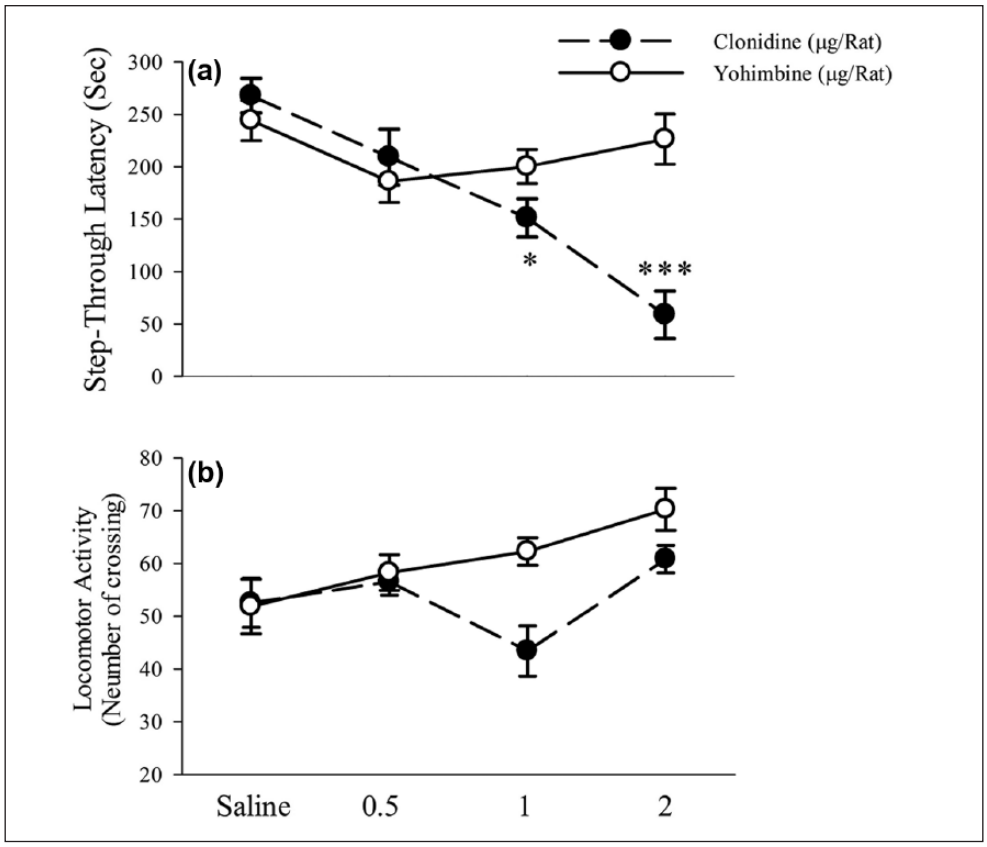

Figure 2. The effects of pre-training intra-medial prefrontal cortex (mPFC) administrations of clonidine and yohimbine on inhibitory avoidance memory acquisition (a) and locomotor activity (b). Eight groups of animals were used. Two groups received saline and the other groups received clonidine or yohimbine at different doses. Values are expressed as mean±standard error of the mean (SEM) (n=8 in each group). *p<0.01 and ***p<0.001 different from saline group.

avoidance memory acquisition (Figure 2(a)), while it does not alter locomotor activity (F(3,28)=2.24, p>0.05) (Figure 2(b)).

Effects of pre-training administration of ACPA on memory acquisition in the absence and presence of clonidine or yohimbine

Results of the two-way ANOVA showed there are significant differences between the groups of animals that received pre-training intra-mPFC administration of clonidine along with ACPA and those which received pre-training injection of vehicle along with ACPA (F dose (3,56)=41.097, p<0.001; F drug (1,56)=69.277, p<0.001; F interaction (3,56)=17.763, p<0.001, (Figure 3(a))) regarding inhibitory avoidance memory, while no significant difference was seen for locomotor activity (F dose (3,56)=2.318, p>0.05; F drug (1,56)=0.001, p>0.05; F interaction (3,56)=2.723, p>0.05, (Figure 3(b))). On the one hand, post-hoc analyses showed that ACPA at the doses of 0.05 and 0.5 µg/rat impairs inhibitory avoidance memory acquisition (Figure 3(a)), while it did not alter locomotor activity (Figure 3(b)) by itself. On the other hand, post-hoc analysis indicated an subthreshold dose of clonidine (0.5 µg/rat) restored ACPA (0.5 and 0.05 µg/rat)-induced memory impairment in the mPFC, while it has no interactive effect on the lower dose of ACPA (0.005 µg/rat).

In addition the two-way ANOVA revealed significant interaction between yohimbine and ACPA on inhibitory avoidance memory acquisition (F dose (3,56)=87.148, p<0.001; F drug (1,56)=3.436, p<0.05; F interaction (3,56)=15.669, p<0.001; (Figure 3(a))), but not on locomotor activity (F dose (3,56)=0.518, p>0.05; F drug (1,56)=0.804, p>0.05; F interaction (3,56)=1.975, p>0.05; (Figure 3(b)). Post-hoc analysis showed that an subthreshold dose of yohimbine (2 µg/rat) potentiated ACPA-induced inhibitory avoidance memory acquisition deficit, when administered together with subthreshold dose of ACPA (0.005 µg/rat), while the intervention has no interactive effect on higher doses of ACPA (0.05 and 0.5 µg/rat).

Effects of SKF96365 on responses induced by co-administration of clonidine or yohimbine with ACPA

One-way ANOVA and post-hoc Tukey's analysis revealed that SKF96365 at the applied dose did not alter memory by itself, while SKF96365 blocked the restoration effect of clonidine (0.5 µg/rat) on ACPA-induced memory deficit and reversed the amnesia induced by yohimbine (2 µg/rat) plus ACPA (0.005 µg/rat) (F(5,42)=24.197, p<0.001); Figure 4). However, it did not alter locomotor activity (F(5,42)=1.598, p>0.05); Figure 4). In

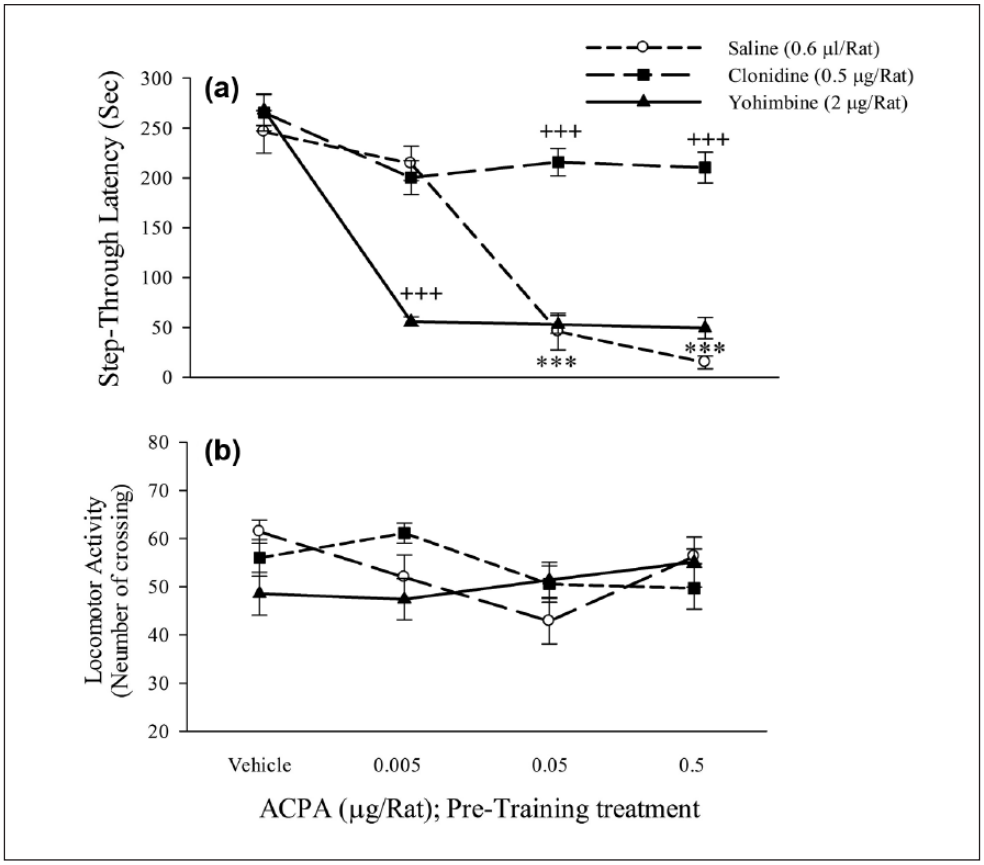

Figure 3. The effects of intra-medial prefrontal cortex (mPFC) co-administration of saline, clonidine or yohimbine plus arachidonylcyclopropylamide (ACPA) on (a) inhibitory avoidance memory acquisition or (b) locomotor activity. Twelve groups of animals were divided into three sets of four groups and received pre-training administration of saline (0.6 µL/rat), clonidine (0.5 µg/rat) or yohimbine (2 µg/rat) plus either vehicle (0.6 µL/rat) or ACPA at different doses (0.005, 0.05, and 0.5 µg/rat). Each bar represents mean±standard error of the mean (SEM) of eight rats per group. ***p<0.001 compared with pre-training vehicle/saline group, +++p<0.001 compared with pre-training saline/ACPA (0.005, 0.05, and 0.5 µg/rat) group.

conclusion, the data demonstrated that clonidine and yohimbine can make their effects on memory acquisition deficit induced by ACPA via Ca^{2+} channels (Figure 4).

Discussion

Our results showed that pre-training intra-mPFC administration of a cannabinoid receptor agonist, ACPA, dose-dependently impairs inhibitory avoidance memory acquisition. These results are in agreement with previous studies that have shown an amnestic effect of CB_1R agonist (Chegini et al., 2014; Yousefi et al., 2013). It has been shown that activation of CB_1Rs impairs all stages of memory, including encoding, consolidation, and retrieval. This could be due to CB_1Rs modulating cAMP-dependent synaptic plasticity (Kim and Thayer, 2000) and altering neurotransmitter release such as glutamate, GABA, glycine, acetylcholine, norepinephrine, dopamine, serotonin, and cholecystokinin (CCK) (Beinfeld and Connolly, 2001; Cadogan et al., 1997; Gifford and Ashby, 1996; Ishac et al., 1996; Jennings et al., 2001; Levenes et al., 1998; Nakazi et al., 2000; Schlicker and Kathmann, 2001; Szabo et al., 1998). Since CB_1Rs are localized to presynaptic axon terminals of many neurons, their activation inhibits the release of neurotransmitters, i.e. GABA and glutamate, as well as that of neuromodulators including acetylcholine, serotonin and noradrenaline that has an important role in the cognitive-related processes (Oropeza et al., 2007).

Our results also revealed the effects of pre-training intra-mPFC administration of alpha-2 adrenoceptor agonist or antagonist on inhibitory avoidance memory. Pre-training intra-mPFC microinjections of an alpha-2 adrenergic agonist, clonidine, at lower doses do not affect the inhibitory avoidance memory acquisition while higher doses of clonidine impaired memory acquisition. On the other hand, yohimbine, an alpha-2 adrenergic receptor antagonist at all doses used did not affect inhibitory avoidance memory acquisition. There are inconsistent results for the activation or blocked of alpha-2 adrenoceptor during memory formation. Some studies have reported that injection of norepinephrine to various brain regions at times when memories are encoded or shortly after the behavioral training could enhance memory performance (McGaugh et al., 1993; Van Stegeren, 2008) and blocked alpha-2 adrenoceptor could have an inhibitory effect on memory (Cahill and McGaugh, 1996; McGaugh, 2004). In contrast, others have reported negative effects of alpha-2 adrenoceptors stimulation on memory performance (Chen et al., 1992; Jafari-Sabet et al., 2013). It has been suggested that the beneficial effect of alpha-2 adrenoceptor agonists on memory are

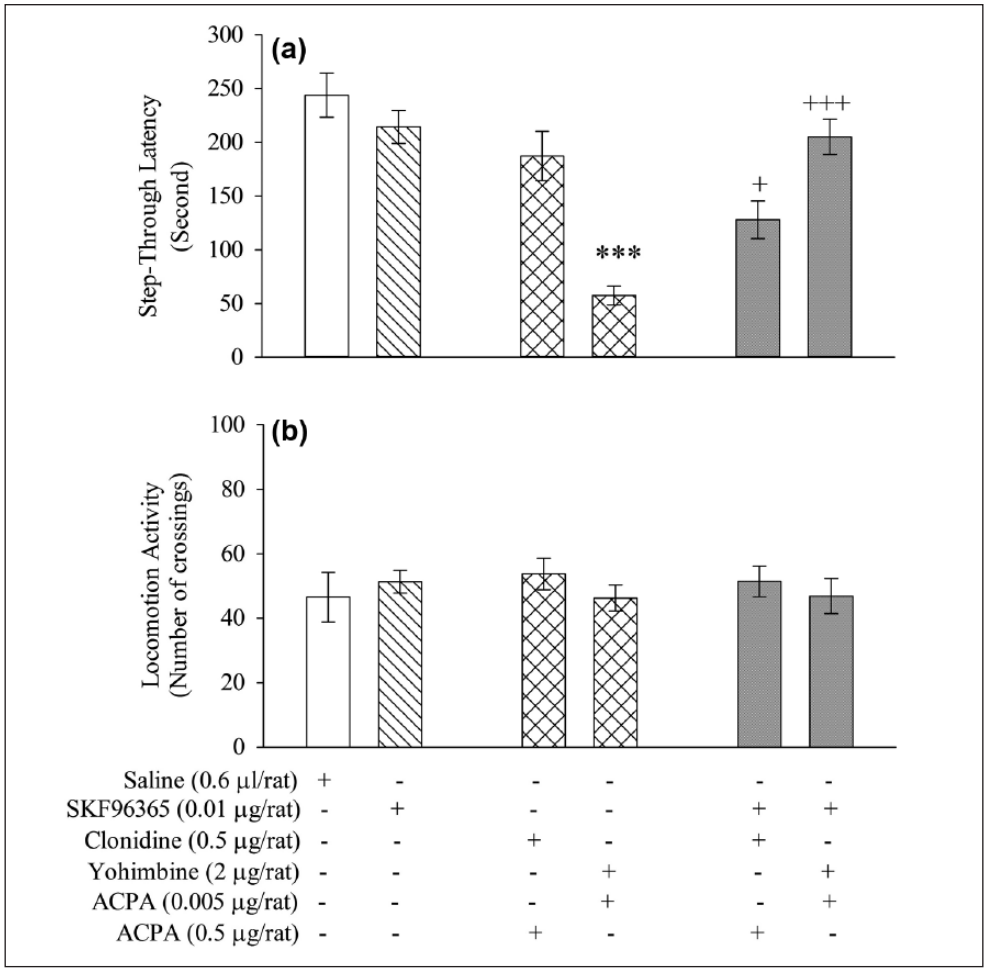

Figure 4. The effect of intra- medial prefrontal cortex (mPFC) injection of SKF96365 in responses-induced by co-administration of clonidine or yohimbine plus arachidonylcyclopropylamide (ACPA). Two groups received saline and SKF96365 (0.1 µg/rat). The other groups received SKF96365 (0.01 µg/rat) 5 min before co-administration of clonidine or yohimbine plus ACPA. Values are expressed as mean±standard error of the mean (SEM) (n=8 in each group). ***p<0.001 compared with saline, +p<0.05, and +++p<0.001 compared with their respective groups.

mediated by the inhibition of hyperpolarization/cyclic nucleotide gated (HCN) channels through inhibition of cAMP/PKA activation in mPFC neurons (Day et al., 2005; Wang et al., 2007) while stimulation of alpha-2 adrenoceptors and inhibition of the cAMP-dependent protein kinase A (PKA) pathway lead to memory impairment in other brain regions such as hippocampus (Abel et al., 1997; Bernabeu et al., 1997; Frey et al., 1993; Tanila, 2001). Accordingly, inhibition of HCN channels may be an important cellular mechanism mediating the enhanced signal to noise ratio produced by noradrenaline in the mPFC and therefore strengthening memory function.

Moreover, our findings provide evidence that alpha-2 adrenoceptors of the mPFC are involved in ACPA-modulated acquisition of inhibitory avoidance memory. Pre-training co-administration of an subthreshold dose of clonidine accompanied with different doses of ACPA prevented the deficit of memory induced by ACPA. In contrast, impairment of memory acquisition was observed following co-administration of an subthreshold dose of yohimbine and also subthreshold dose of ACPA.

Some studies have shown functional interactions between cannabinoids and central noradrenergic systems (Carvalho et al., 2010; Mendiguren and Pineda, 2006; Muntoni et al., 2006; Oropeza et al., 2007; Page et al., 2008). Most studies on the interactions between the cannabinoid and adrenergic systems have concentrated on the inhibitory effect of presynaptic CB_1Rs on noradrenergic neurotransmission (Hudson et al., 2010). In this regard, it has been reported that CB_1Rs are localized on presynaptic noradrenergic axon terminals in the mPFC (Oropeza et al., 2007) that contribute to regulation of norepinephrine release. On the other hand, it has been reported that idazoxan (a selective alpha-2 adrenoceptor antagonist) triggered a decrease in density of CB_1Rs in the mPFC, indicating that high extracellular level of norepinephrine down-regulates CB_1Rs. Richter et al. (2012) have reported that endogenously or exogenously activated alpha-2 adrenoceptors in the same presynaptic compartment occlude the inhibitory action CB_1Rs. Moreover, evidence has reported that after chronic WIN55, 212-2 (a CB_1R agonist) exposure followed by a period of drug discontinuation, anxiety-like behavior and noradrenaline levels return to control levels (Page et al., 2008). This effect could be blocked by SR141716A (a CB_1R antagonist). Interestingly, administration of SR141716A alone significantly reduced LC spontaneous firing, showing that endogenous

cannabinoid tone controls LC activity (Carvalho and Van Bockstaele, 2012). Unfortunately, few studies have focused on the interaction of cannabinoids and norepinephrine on the cellular level, although there are abundant data about the action of cannabinoids on complex changes of behavior mediated by the monoaminergic system. Several potential mechanisms have been suggested for the interactions between alpha-2 adrenoceptors and CB_1Rs: (a) utilization of a common Gi/o pool and subsequent downstream signaling cascades; (b) agonist-induced heterologous desensitization through internalization and nonfunctional receptor production by phosphorylation; (c) heterodimeric interaction between alpha-2 adrenoceptors and CB_1Rs (Richter et al., 2012). According to the neuroanatomical data, dopamine-β-hydroxylase (DβH) positive varicose axon terminals of the mPFC express CB_1R immunoreactivity (Oropeza et al., 2007), although most CB_1Rs are predominantly of putative GABAergic and glutamatergic nature in cortical regions (Bodor et al., 2005; Ferreira et al., 2012; Lafourcade et al., 2007). It has been shown that presynaptic CB_1R activation decreases the release probability of both GABA and glutamate (Ferreira et al., 2012; Lafourcade et al., 2007). The net outcome of CB_1R activation in cortical layers II/III is the increase of pyramidal neuron firing (Fortin et al., 2004), but in the layer V, CB_1R activation decreases pyramidal neuron firing (Fortin and Levine, 2007). And when referring to extracellular glutamate concentration – it is important to say "extracellular". The above studies did not measure extracellular glutamate concentrations, and extracellular glutamate is a result of spill-over, that is, abnormal glutamatergic firing leads to so much extracellular glutamate which overwhelms the astrocytic reuptake system.

At the functional level, clonidine can prevent the working memory impairment caused by an inverse agonist acting upon the GABA-A receptor (Jentsch et al., 2008; Murphy et al., 1996). Accordingly alpha-2 adrenoceptor agonists might balance the effects of GABA insufficiency. Furthermore glutamate synaptic transmission in the mPFC is suppressed by stimulation of alpha-2 adrenoceptors (Ji et al., 2008). Therefore, there is a possibility that alpha-2 adrenoceptor agonists enhance memory performance via actions at alpha-2 adrenoceptors on non-adrenergic cells.

We also used SKF96365, a blocker of voltage-activated T-type Ca^{2+} channel (Ahmadi et al., 2013; Khanegheini et al., 2015) to analyze whether Ca^{2+} is involved in alpha-2 adrenoceptor effects. Our results showed that SKF96365 at the applied dose did not alter memory by itself, while it reduced the effects of clonidine on ACPA-induced memory deficit and reversed the amnesia induced by co-administration of ACPA plus yohimbine in the mPFC, suggesting involvement of the Ca^{2+} channel in this phenomenon at alpha-2 adrenoceptors.

Ca^{2+} influx through pre-synaptic voltage-gated Ca^{2+} channels initiates release of neurotransmitters (Catterall and Few, 2008). These channels are expressed on pre-synaptic noradrenergic neurons in the LC, and also on pyramidal cells in the mPFC (Steenland et al., 2006). Alpha-2 adrenoceptor agonists inhibit these channels via inhibition of adenylate cyclase, which can lead to reduction of neurotransmitter release (Debock et al., 2003; Timmons et al., 2004).

Briefly, responses mediated through alpha adrenoceptors are dependent on Ca^{2+} fluxes and it has been suggested that the alpha-2 adrenoceptor is particularly associated with the influx of extracellular Ca^{2+} ions, which is preferentially antagonized by Ca^{2+} channel blocking drugs.

Conclusion

Our data indicated that intimate interactions between alpha-2 adrenergic and CB_1Rs exist within the mPFC and that the alpha-2 adrenergic receptor mechanism, at least partly, is involved in modulating ACPA effect on memory acquisition in this region. In addition, current study revealed that Ca^{2+} channel blockade by SKF96365 could inhibit the neurotransmitter exocytosis from pre-synaptic neurons, indicating involvement of mPFC Ca^{2+} signaling in the pre-synaptic alpha-2 adrenergic receptors modulation of inhibitory avoidance memory deficits induced by ACPA.

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References

Abel T, Nguyen PV, Barad M, et al. (1997) Genetic demonstration of a role for PKA in the late phase of LTP and in hippocampus-based long-term memory. *Cell* 88: 615–626.

Adams IB and Martin BR (1996) Cannabis: Pharmacology and toxicology in animals and humans. *Addiction* 91: 1585–1614.

Ahmadi H, Nasehi M, Rostami P, et al. (2013) Involvement of the nucleus accumbens shell dopaminergic system in prelimbic NMDA-induced anxiolytic-like behaviors. *Neuropharmacology* 71: 112–123.

Al-Hayani A and Davies SN (2002) Effect of cannabinoids on synaptic transmission in the rat hippocampal slice is temperature-dependent. *Eur J Pharmacol* 442: 47–54.

Arnsten A and Goldman-Rakic PS (1985) Alpha 2-adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. *Science* 230: 1273–1276.

Arnsten A, Cai JX and Goldman-Rakic PS (1988) The alpha-2 adrenergic agonist guanfacine improves memory in aged monkeys without sedative or hypotensive side effects: Evidence for alpha-2 receptor subtypes. *J Neurosci* 8: 4287–4298.

Beinfeld MC and Connolly K (2001) Activation of CB_1 cannabinoid receptors in rat hippocampal slices inhibits potassium-evoked cholecystokinin release, a possible mechanism contributing to the spatial memory defects produced by cannabinoids. *Neurosci Lett* 301: 69–71.

Bernabeu R, Bevilaqua L, Ardenghi P, et al. (1997) Involvement of hippocampal cAMP/cAMP-dependent protein kinase signaling pathways in a late memory consolidation phase of aversively motivated learning in rats. *Proc Natl Acad Sci U S A* 94: 7041–7046.

Bisogno T, Berrendero F, Ambrosino G, et al. (1999) Brain regional distribution of endocannabinoids: Implications for their biosynthesis and biological function. *Biochem Biophys Res Commun* 256: 377–380.

Bodor ÁL, Katona I, Nyíri G, et al. (2005) Endocannabinoid signaling in rat somatosensory cortex: Laminar differences and involvement of specific interneuron types. *J Neurosci* 25: 6845–6856.

Cadogan AK, Alexander SP, Boyd EA, et al. (1997) Influence of cannabinoids on electrically evoked dopamine release and cyclic AMP generation in the rat striatum. *J Neurochem* 69: 1131–1137.

Cahill L and McGaugh JL (1996) The neurobiology of memory for emotional events: adrenergic activation and the amygdala. *Proc West Pharmacol Soc* 39: 81–84.

Cai JX, Ma Y-Y, Xu L, et al. (1993) Reserpine impairs spatial working memory performance in monkeys: Reversal by the α2-adrenergic agonist clonidine. *Brain Res* 614: 191–196.

Carvalho AF and Van Bockstaele EJ (2012) Cannabinoid modulation of noradrenergic circuits: Implications for psychiatric disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 38: 59–67.

Carvalho AF, Mackie K and Van Bockstaele EJ (2010) Cannabinoid modulation of limbic forebrain noradrenergic circuitry. *Eur J Neurosci* 31: 286–301.

Castillo PE, Younts TJ, Chávez AE, et al. (2012) Endocannabinoid signaling and synaptic function. *Neuron* 76: 70–81.

Cathel AM, Reyes BA, Wang Q, et al. (2014) Cannabinoid modulation of alpha2 adrenergic receptor function in rodent medial prefrontal cortex. *Eur J Neurosci* 40: 3202–3214.

Catterall WA and Few AP (2008) Calcium channel regulation and presynaptic plasticity. *Neuron* 59: 882–901.

Cecchi M, Khoshbouei H and Morilak DA (2002) Modulatory effects of norepinephrine, acting on alpha1 receptors in the central nucleus of the amygdala, on behavioral and neuroendocrine responses to acute immobilization stress. *Neuropharmacology* 43: 1139–1147.

Chegini H-R, Nasehi M and Zarrindast M-R (2014) Differential role of the basolateral amygdala 5-HT3 and 5-HT4 serotonin receptors upon acpa-induced anxiolytic-like behaviors and emotional memory deficit in mice. *Behav Brain Res* 261: 114–126.

Chen M, Chiu T and Lee E (1992) Noradrenergic mediation of the memory-enhancing effect of corticotropin-releasing factor in the locus coeruleus of rats. *Psychoneuroendocrinology* 17: 113–124.

Collins DR, Pertwee RG and Davies SN (1994) The action of synthetic cannabinoids on the induction of long-term potentiation in the rat hippocampal slice. *Eur J Pharmacol* 259: R7–R8.

Coulston CM, Perdices M, Henderson AF, et al. (2011) Cannabinoids for the treatment of schizophrenia? A balanced neurochemical framework for both adverse and therapeutic effects of cannabis use. *Schizophr Res Treatment* 2011: 501726.

Davis M, Rainnie D and Cassell M (1994) Neurotransmission in the rat amygdala related to fear and anxiety. *Trends Neurosci* 17: 208–214.

Day M, Carr DB, Ulrich S, et al. (2005) Dendritic excitability of mouse frontal cortex pyramidal neurons is shaped by the interaction among HCN, Kir2, and Kleak channels. *J Neurosci* 25: 8776–8787.

Debock F, Kurz J, Azad S, et al. (2003) A2-adrenoreceptor activation inhibits LTP and LTD in the basolateral amygdala: Involvement of Gi/O-protein-mediated modulation of Ca2+-channels and inwardly rectifying K+-channels in ltd. *Eur J Neurosci* 17: 1411–1424.

Di Marzo V, Hill MP, Bisogno T, et al. (2000) Enhanced levels of endogenous cannabinoids in the globus pallidus are associated with a reduction in movement in an animal model of Parkinson's disease. *FASEB J* 14: 1432–1438.

Ferreira SG, Teixeira FM, Garção P, et al. (2012) Presynaptic CB_1 cannabinoid receptors control frontocortical serotonin and glutamate release–species differences. *Neurochem Int* 61: 219–226.

Ferry B, Magistretti PJ and Pralong E (1997) Noradrenaline modulates giutamate-mediated neurotransmission in the rat basolateral amygdala in vitro. *Eur J Neurosci* 9: 1356–1364.

Fišar Z (2012) Cannabinoids and monoamine neurotransmission with focus on monoamine oxidase. *Prog Neuropsychopharmacol Biol Psychiatry* 38: 68–77.

Fortin DA and Levine ES (2007) Differential effects of endocannabinoids on glutamatergic and gabaergic inputs to layer 5 pyramidal neurons. *Cereb Cortex* 17: 163–174.

Fortin DA, Trettel J and Levine ES (2004) Brief trains of action potentials enhance pyramidal neuron excitability via endocannabinoid-mediated suppression of inhibition. *J Neurophysiol* 92: 2105–2112.

Franowicz JS, Kessler LE, Borja CMD, et al. (2002) Mutation of the A2a-adrenoceptor impairs working memory performance and annuls cognitive enhancement by guanfacine. *J Neurosci* 22: 8771–8777.

Frey U, Huang Y and Kandel E (1993) Effects of cAMP simulate a late stage of LTP in hippocampal CA_1 neurons. *Science* 260: 1661–1664.

Gifford AN and Ashby C (1996) Electrically evoked acetylcholine release from hippocampal slices is inhibited by the cannabinoid receptor agonist, Win 55212–2, and is potentiated by the cannabinoid antagonist, Sr 141716a. *J Pharmacol Exp Ther* 277: 1431–1436.

Glass M, Faull R and Dragunow M (1997) Cannabinoid receptors in the human brain: A detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience* 77: 299–318.

Gold PE (1986) The use of avoidance training in studies of modulation of memory storage. *Behav Neural Biol* 46: 87–98.

Hampson RE, Simeral JD and Deadwyler SA (1999) Distribution of spatial and nonspatial information in dorsal hippocampus. *Nature* 402: 610–614.

Hatfield T and McGaugh JL (1999) Norepinephrine infused into the basolateral amygdala posttraining enhances retention in a spatial water maze task. *Neurobiol Learn Mem* 71: 232–239.

Hoffman BM, Papas RK, Chatkoff DK, et al. (2007) Meta-analysis of psychological interventions for chronic low back pain. *Health Psychol* 26: 1–9.

Hosseini N, Nasehi M, Radahmadi M, et al. (2013) Effects of CA_1 glutamatergic systems upon memory impairments in cholestatic rats. *Behav Brain Res* 256: 636–645.

Howlett AC, Barth F, Bonner TI, et al. (2002) International Union of Pharmacology. Xxvii. Classification of cannabinoid receptors. *Pharmacol Rev* 54: 161–202.

Hudson BD, Hébert TE and Kelly ME (2010) Physical and functional interaction between CB_1 cannabinoid receptors and B2-adrenoceptors. *Br J Pharmacol* 160: 627–642.

Ishac EJ, Jiang L, Lake KD, et al. (1996) Inhibition of exocytotic noradrenaline release by presynaptic cannabinoid CB_1 receptors on peripheral sympathetic nerves. *Br J Pharmacol* 118: 2023–2028.

Jafari-Sabet M, Banafshe HR and Khodadadnejad M-A (2013) Modulation of muscimol state-dependent memory by A2-adrenoceptors of the dorsal hippocampal area. *Eur J Pharmacol* 710: 92–99.

Jamali-Raeufy N, Nasehi M and Zarrindast MR (2011) Influence of N-methyl D-aspartate receptor mechanism on Win55, 212–2-induced amnesia in rat dorsal hippocampus. *Behav Pharmacol* 22: 645–654.

Jennings E, Vaughan C and Christie M (2001) Cannabinoid actions on rat superficial medullary dorsal horn neurons in vitro. *J Physiol* 534: 805–812.

Jentsch JD and Anzivino LA (2004) A low dose of the alpha2 agonist clonidine ameliorates the visual attention and spatial working memory deficits produced by phencyclidine administration to rats. *Psychopharmacology* 175: 76–83.

Jentsch JD, Sanchez D, Elsworth JD, et al. (2008) Clonidine and guanfacine attenuate phencyclidine-induced dopamine overflow in rat prefrontal cortex: Mediating influence of the alpha-2a adrenoceptor subtype. *Brain Res* 1246: 41–46.

Ji X-H, Ji J-Z, Zhang H, et al. (2008) Stimulation of A2-adrenoceptors suppresses excitatory synaptic transmission in the medial prefrontal cortex of rat. *Neuropsychopharmacology* 33: 2263–2271.

Jin X, Ma C and Li B (2007) The alpha 2a-adrenoceptor agonist guanfacine improves spatial learning but not fear conditioning in rats. *Sheng Li Xue Bao* 59: 739.

Khakpai F, Nasehi M, Haeri-Rohani A, et al. (2012) Scopolamine induced memory impairment; possible involvement of NMDA receptor mechanisms of dorsal hippocampus and/or septum. *Behav Brain Res* 231: 1–10.

Khanegheini A, Nasehi M and Zarrindast M-R (2015) The modulatory effect of CA_1 GABAb receptors on ketamine-induced spatial and

non-spatial novelty detection deficits with respect to Ca 2+. *Neuroscience* 305: 157–168.
Kim DJ and Thayer SA (2000) Activation of CB_1 cannabinoid receptors inhibits neurotransmitter release from identified synaptic sites in rat hippocampal cultures. *Brain Res* 852: 398–405.
Lafourcade M, Elezgarai I, Mato S, et al. (2007) Molecular components and functions of the endocannabinoid system in mouse prefrontal cortex. *PloS One* 2: e709.
Lechner SG, Hussl S, Schicker KW, et al. (2005) Presynaptic inhibition via a phospholipase C-and phosphatidylinositol bisphosphate-dependent regulation of neuronal Ca2+ channels. *Mol Pharmacol* 68: 1387–1396.
Levenes C, Daniel H, Soubrie P, et al. (1998) Cannabinoids decrease excitatory synaptic transmission and impair long-term depression in rat cerebellar Purkinje cells. *J Physiol* 510: 867–879.
Levy F (2008) Pharmacological and therapeutic directions in ADHD: Specificity in the PFC. *Behav Brain Funct* 4: 12.
Li B-M, Mao Z-M, Wang M, et al. (1999) Alpha-2 adrenergic modulation of prefrontal cortical neuronal activity related to spatial working memory in monkeys. *Neuropsychopharmacology* 21: 601–610.
Liang K, Juler RG and McGaugh JL (1986) Modulating effects of post-training epinephrine on memory: Involvement of the amygdala noradrenergic system. *Brain Res* 368: 125–133.
Lichtman AH, Dimen KR and Martin BR (1995) Systemic or intrahippocampal cannabinoid administration impairs spatial memory in rats. *Psychopharmacology* 119: 282–290.
McCann DJ, Rabin RA and Winter J (1987) Interactions of clonidine with phencyclidine and ketamine: Studies of radial maze performance and righting reflex in rats. *Pharmacol Biochem Behav* 26: 23–28.
McGaugh JL (2004) The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu Rev Neurosci* 27: 1–28.
McGaugh JL, Introini-Collison IB, Cahill LF, et al. (1993) Neuromodulatory systems and memory storage: Role of the amygdala. *Behav Brain Res* 58: 81–90.
Marrs W, Kuperman J, Avedian T, et al. (2005) Alpha-2 adrenoceptor activation inhibits phencyclidine-induced deficits of spatial working memory in rats. *Neuropsychopharmacology* 30: 1500–1510.
Marsicano G, Wotjak CT, Azad SC, et al. (2002) The endogenous cannabinoid system controls extinction of aversive memories. *Nature* 418: 530–534.
Mendiguren A and Pineda J (2006) Systemic effect of cannabinoids on the spontaneous firing rate of locus coeruleus neurons in rats. *Eur J Pharmacol* 534: 83–88.
Misner DL and Sullivan JM (1999) Mechanism of cannabinoid effects on long-term potentiation and depression in hippocampal CA_1 neurons. *J Neurosci* 19: 6795–6805.
Mohammadi M, Nasehi M and Zarrindast M-R (2015) Modulation of the effects of the cannabinoid agonist, ACPA, on spatial and non-spatial novelty detection in mice by dopamine D1 receptor drugs infused into the basolateral amygdala. *Behav Brain Res* 280: 36–44.
Montgomery C and Fisk JE (2007) Everyday memory deficits in ecstasy-polydrug users. *J Psychopharmacol* 21: 709–717.
Muntoni AL, Pillolla G, Melis M, et al. (2006) Cannabinoids modulate spontaneous neuronal activity and evoked inhibition of locus coeruleus noradrenergic neurons. *Eur J Neurosci* 23: 2385–2394.
Murphy BL, Arnsten AF, Jentsch JD, et al. (1996) Dopamine and spatial working memory in rats and monkeys: Pharmacological reversal of stress-induced impairment. *J Neurosci* 16: 7768–7775.
Nakazi M, Bauer U, Nickel T, et al. (2000) Inhibition of serotonin release in the mouse brain via presynaptic cannabinoid CB_1 receptors. *Naunyn Schmiedebergs Arch Pharmacol* 361: 19–24.
Nasehi M, Sahebgharani M, Haeri-Rohani A, et al. (2009) Effects of cannabinoids infused into the dorsal hippocampus upon memory formation in 3-days apomorphine-treated rats. *Neurobiol Learn Mem* 92: 391–399.
Niyuhire F, Varvel SA, Thorpe AJ, et al. (2007) The disruptive effects of the CB_1 receptor antagonist rimonabant on extinction learning in mice are task-specific. *Psychopharmacology* 191: 223–231.
Oropeza VC, Mackie K and Van Bockstaele EJ (2007) Cannabinoid receptors are localized to noradrenergic axon terminals in the rat frontal cortex. *Brain Res* 1127: 36–44.
Page M, Oropeza V and Van Bockstaele E (2008) Local administration of a cannabinoid agonist alters norepinephrine efflux in the rat frontal cortex. *Neurosci Lett* 431: 1–5.
Paxinos G and Franklin KB (2004) *The Mouse Brain in Stereotaxic Coordinates*. San Diego, CA: Elsevier.
Piri M and Zarrindast MR (2011) Modulation of Win55, 212–2 state-dependent memory by A2-adrenergic receptors of the dorsal hippocampus. *Arch Iran Med* 14: 389–395.
Puighermanal E, Busquets-Garcia A, Gomis-González M, et al. (2013) Dissociation of the pharmacological effects of THC by MTOR blockade. *Neuropsychopharmacology* 38: 1334–1343.
Ranganathan M and D'Souza DC (2006) The acute effects of cannabinoids on memory in humans: A review. *Psychopharmacology* 188: 425–444.
Rasekhi K, Oryan S, Nasehi M, et al. (2014) Involvement of the nucleus accumbens shell glutamatergic system in ACPA-induced impairment of inhibitory avoidance memory consolidation. *Behav Brain Res* 269: 28–36.
Richter H, Teixeira FM, Ferreira SG, et al. (2012) Presynaptic A 2-adrenoceptors control the inhibitory action of presynaptic Cb 1 cannabinoid receptors on prefrontocortical norepinephrine release in the rat. *Neuropharmacology* 63: 784–797.
Riedel G and Davies SN (2005) Cannabinoid function in learning, memory and plasticity. *Handb Exp Pharmacol*: 445–477.
Rossetti ZL and Carboni S (2005) Noradrenaline and dopamine elevations in the rat prefrontal cortex in spatial working memory. *J Neurosci* 25: 2322–2329.
Schlicker E and Kathmann M (2001) Modulation of transmitter release via presynaptic cannabinoid receptors. *Trends Pharmacol Sci* 22: 565–572.
Solowij N and Battisti R (2008) The chronic effects of cannabis on memory in humans: A review. *Curr Drug Abuse Rev* 1: 81–98.
Steenland HW, Ko SW, Wu L-J, et al. (2006) Hot receptors in the brain. *Mol Pain* 2: 1.
Suzuki A, Josselyn SA, Frankland PW, et al. (2004) Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *J Neurosci* 24: 4787–4795.
Szabo B, Dörner L, Pfreundtner C, et al. (1998) Inhibition of GABAergic inhibitory postsynaptic currents by cannabinoids in rat corpus striatum. *Neuroscience* 85: 395–403.
Tanila H (2001) Noradrenergic regulation of hippocampal place cells. *Hippocampus* 11: 793–808.
Terranova J-P, Michaud J-C, Le Fur G, et al. (1995) Inhibition of long-term potentiation in rat hippocampal slices by anandamide and Win55212–2: Reversal by Sr141716a, a selective antagonist of CB_1 cannabinoid receptors. *Naunyn Schmiedebergs Arch Pharmacol* 352: 576–579.
Timmons S, Geisert E, Stewart A, et al. (2004) A 2-adrenergic receptor-mediated modulation of calcium current in neocortical pyramidal neurons. *Brain Res* 1014: 184–196.
Torkaman-Boutorabi A, Sheidadoust H, Hashemi-Hezaveh S-M, et al. (2015) Influence of morphine on medial prefrontal cortex alpha2 adrenergic system in passive avoidance learning in rats. *Pharmacol Biochem Behav*133: 92–98.
Tsou K, Brown S, Sanudo-Pena M, et al. (1998) Immunohistochemical distribution of cannabinoid CB_1 receptors in the rat central nervous system. *Neuroscience* 83: 393–411.
Van Stegeren AH (2008) The role of the noradrenergic system in emotional memory. *Acta Psychol (Amst)* 127: 532–541.
Wang M, Ramos BP, Paspalas CD, et al. (2007) A2a-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. *Cell* 129: 397–410.
Yousefi B, Farjad M, Nasehi M, et al. (2013) Involvement of the CA_1 GABA a receptors in ACPA-induced impairment of spatial and non-spatial novelty detection in mice. *Neurobiol Learn Mem* 100: 32–40.