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Influence of ACPA in the Dorsal Hippocampus on Muscimol state - dependent, learning in the inhibitory Avoidance Task

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ABSTRACT: Learning and memory are the complicated agents of central nervous system that various regions of brain can be involved in these phenomena, especially regions like hippocamp. Various agents like cannabinoid and GABA can influence learning and memory. In the present study, the effect of cannabinoid receptors agonist, ACPA, on muscimol induced state-dependent memory examined. Cannabinoids cause a wide array of effects in different species. Their effects are mainly produced through cannabinoid receptors; CB1and CB2 subtypes. The CB1 receptors are densely expressed in areas classically involved in learning and memory. In rodents, the CB1 receptor is almost exclusively expressed by GABAergic interneurons in the neocortex, amygdala and hippocampus. This unique localization of CB1 receptors points to the existence of functional interactions between the cannabinoid and GABAergic systems. Indeed, activation of cannabinoid receptors generally results in the inhibition of ongoing neurotransmitter release, including GABA. The step-through passive avoidance paradigm used in the present study is an accepted model to examine long-term memory in male Wistar rats. Pre-training intra-CA1 administration of muscimol (0.15µg/rat) decreased the memory retrieval. Pre-test muscimol (0.15µg/rat) administration restored the retrieval to the control level in the test day. This phenomenon is known as muscimol state-dependent. Administration of ACPA (0.5 µg/rat, intra - CA1) 5 min before test by itself decreased the memory retrieval. On the other hands, the animals in which memory retrieval was impaired, due to muscimol) 0.15µg/rat (pre-training administration, pre-test administration of ACPA (0.5µg/rat, intra-CA1) 24 hr after training in day's test restored memory. The results suggest that cannabinoid receptors of the dorsal hippocampal CA1 regions may play an important role in muscimol - induced amnesia and muscimol state- dependent memory.

Keyword: Muscimol, ACPA, state- dependent memory, passive avoidance task, rat.

INTRODUCTION

Memories especially those of emotional types, can depend on an endogenous state of subjects; this phenomenon is termed state-dependence(Barros et al. 2000; McGaugh 2005). In a state-dependent memory when pre- or post-training administrations of a drug decrease memory for a task, administration of the drug prior to testing retards the extinction of the task (Overton 1991). According to previous researches, variety of drugs can induce state-dependent memory in laboratory animals (Izquierdo and Dias 1983). Cannabinoids has also been shown to induce state-dependent memory. Either pre- or post-training administrations of a potent synthetic cannabinoid receptor agonist, WIN55,212-2, impaired retrieval of learned tasks, which was reversible by pre-test administration of the drug (Zarrindast *et al.* 2006; Nasehi *et al.* 2009a). Cannabinoids, as psychoactive drugs cause different effects in a large number of species. The agents exert their effects through two different CB1 (Matsuda *et al.* 1990) and CB2 (Munro *et al.* 1993).

cannabinoid receptor subtypes. The CB1 receptors are mainly found in the central nervous system, but they are also found in peripheral tissues (Svizenska *et al.* 2008). However, there is a report that CB2 receptors existed only in the periphery, but CB2 receptors have been found in the brain areas such as the hippocampus(Mackie and Stella 2006; Brusco *et al.* 2008). Although, the existence of a non-CB1/ CB2 (so-called CB3) receptor in mouse hippocampus has been suggested (Hajos and Freund 2002), but has been denied by other investigators (Kawamura et al. 2006; Takahashi and Castillo 2006).

Cannabinoid receptors are widely distributed in the hippocampus, cortex, basal ganglia and the cerebellum (Davies *et al.* 2002). There are high levels of expression of CB1 receptors in the hippocampal formation (Hampson and Deadwyler 1999). Cannabinoid CB1 receptor agonists reduce the release of neurotransmitters such as serotonin(Molina-Holgado *et al.* 1996), GABA (Garcia-Gil *et al.* 1999), opioids (Vela *et al.* 1998a) and dopamine (Schlicker *et al.* 1996), which may lead to substantial and long-lasting changes in different behavioural patterns (Fernandez-Ruiz *et al.* 2000; Viveros *et al.* 2005). Cannabinoids may have interactions with several neurotransmitter systems, including the dopaminergic(Bormann 2000), the serotonergic (Molina-Holgado *et al.* 1996), the GABAergic (Garcia-Gil *et al.* 1999), the opioidergic(Vela *et al.* 1998a) and nitric oxide (Emson 2007) leading to substantial and long-lasting changes in different behavioral patterns(Reis *et al.* 2009) .

Themajor inhibitory neurotransmitter, γ-aminobutyric acid (GABA) exists in the mammalian brain (Watanabe *et al.* 2002). It inhibits neuronal activity through three different GABA receptors; GABA-A and GABA-C receptor subtypes are associated with ligand gated chloride channels, whereas GABA-B receptors are linked to G-proteins (Lee *et al.* 2009) . Previously, the influence of the GABAergic system on learning and memory retention had been demonstrated (Nakagawa *et al.* 1999). The administration of GABAergic receptor agonists, while their antagonists facilitate memory storage and retrieval in inhibitory avoidance tasks (Castellano *et al.* 1989). GABA plays a controlling role on the balance of excitability and inhibitory states in the cortex, hippocampus and the interneurons and is involved in information processing in the hippocampus. On the other hand, GABA-ergic neurons in the hippocampus are involved in the learning and memory (Paulsen and Moser 1998).

MATERIALS AND METHOD

Animals. Adult male Wistar rats (Pasteur Institute, Tehran, Iran), weighing 200-250 g at the beginning of the experiments, were used. All rats were maintained, upon their arrival, in the laboratory (1 week before the experiments) in groups of four in each cage, with food and water freely available. The subjects were kept at a constant temperature of 22±21°C and maintained under a 12/12-h light-dark cycle, with lights on at 07:00 h. The experiments were carried out during the light phase between 08:00 and 12:00 h.

All experimental groups consisted of eight subjects and each subject was tested once. All procedures were performed in accordance with institutional guidelines for animal care and use.

Surgery. Subjects were anaesthetized in traperitoneally with aketamine/xylazine mixture (100 and 10 mg/kg, respectively) and placed in a stereotaxic frame (David Kopf Instruments, Tujunga, California, USA) in a flat-skull position [incisor bar - 3.3mm relative to the interaural line (Paxinos and Watson, 2006)]. A midline incision was made and the skin and underlying periosteum retracted. Bilateral stainless steel guide cannulae (22 gauge, outer and inner diameter = 0.71mm and 0.41 mm, respectively) were implanted 2mm above the Hippocampus according to stereotaxic coordinates: anterior-posterior, -2mm forward of bregma; lateral, ±1.6 mm from midline; ventral, - 1.5mm relative to the dura (Paxinos and Watson, 2006), and anchored to the skull with a jeweler's screw and dental cement. Stainless steel stylets (27 gauge; outer and inner diameter = 0.41mm and 0.2 mm, respectively) were inserted into the guide cannulae to maintain patency before microinjections.

Drugs and microinjections. The drugs included muscimol (Sigma, Poole, Dorset, UK), and ACPA (Tocris, Bristol, UK). All drugs were dissolved in sterile saline. Bilateral microinfusions of nicotine and muscimol into the hippocampus were in a volume of 0.6 ml (0.3 ml per each side). Intra-hippocamp injections of the drugs or saline were given by lowering a 27-gauge injector cannula (outer and inner diameter=0.41 and 0.2 mm, respectively) to extend 2mm beyond the tip of the guide cannulae to the site of infusion (-1.5mm from the skull). The injector cannula was attached, by a polyethylene tube, to a 1-ml Hamilton syringe. Infusion time was 60 s followed by additional 60 s after the injection to facilitate diffusion of the drugs from the tip of the injector cannula. The rationale for using the drug doses was based on a pilot study and earlier studies from our laboratory (Ahmadi e*t al.* 2007a; Mahmoodi *et al.* 2010).

Inhibitory (passive) avoidance apparatus. The inhibitory avoidance apparatus consisted of two compartments of the same size (20-20-30 cm), divided by a wall, in the middle of which was a guillotine door (7-9 cm) that could be lifted manually. The walls and floor of one compartment consisted of white opaqueresin and were lit with a 20W electric bulb placed approximately 50 cm above the floor of the apparatus, the walls of the other compartment were dark.

Stainless steel grids (0.3mm in diameter) were placed at 1-cm intervals (distance between the centres of the grids) on the floor of the dark compartment. Intermittent electric shocks (50 Hz, 3s, 1mA intensity) were delivered to the grid floor of the dark compartment by an isolated stimulator.

Behavioural procedures. Training. Training procedures were based on our earlier studies (Ahmadi *et al.* 2007b). All subjects were allowed to habituate in the experimental room (with light and sound attenuated) for at least 30 min before experiments. Then, each subject was gently placed in the brightly lit compartment of the apparatus; after 5 s the guillotine door was opened and the subject was allowed to enter the dark compartment. The latency with which the subject entered the dark compartment was recorded. Subjects that waited for more than 100 s to enter the dark compartment were eliminated from the experiments (in these experiments, all the subjects reach the above criterion). Once the subject entered the next compartment with all four paws, the guillotine door was closed and the rat was returned to its home cage. The trial was repeated after 30 min. After 5 s the guillotine door was opened and as soon as the subject entered the dark (shock) compartment the door was closed and a foot shock (50 Hz, 1mA and 3 s) was immediately delivered to the grid floor of the compartment. After 20 s, the rat was removed from the apparatus and placed temporarily in its home cage. Two minutes later, the subject was retested in the same way as the earlier trials and if the rat did not enter the dark compartment during 120 s successful acquisition of passive avoidance response was recorded. Otherwise, when the rat entered the dark compartment (before 120 s), the door was closed and again the subject received the same shock similar to the first trial. In this study about 10% of rats received two trials, but no rats received more than two trials. After retesting, the subject was removed from the apparatus and received post-training injection of drugs.

Testing. Twenty four hours after the training session each subject was gently placed in the light compartment and after 5 s the door was opened, and the step-through latency with which the subject entered the dark compartment was measured. The testing session was ended when the subject entered the dark compartment or remained in the light compartment for 300 s. During testing sessions no electric shock was applied.

Data analiysis. The data are expressed as mean ± SEM. The statistical analysis was performed using one- and two-way analysis of variance (ANOVA). Post-hoc comparison of means was carried out with the Tukey test for multiple comparisons, when appropriate. The level of statistical significance was set at $P < 0.05$. Calculations were performed using the SPSS statistical package.

Histology. After the testing sessions, each rat was deeply anaesthetized and 0.6 ml of a 4% methylene blue solution was bilaterally infused into the hippocamp (0.3 ml/each side), as described in Drug section, decapitated and its brain removed and placed in formaldehyde (10%). After several days, the brains were sliced and the sites of injections were verified according to Paxinos and Watson (2006). Data from rats with incorrect placement were excluded from the analysis. Fig. 1 shows a histological presentation of a typical cannula placement.

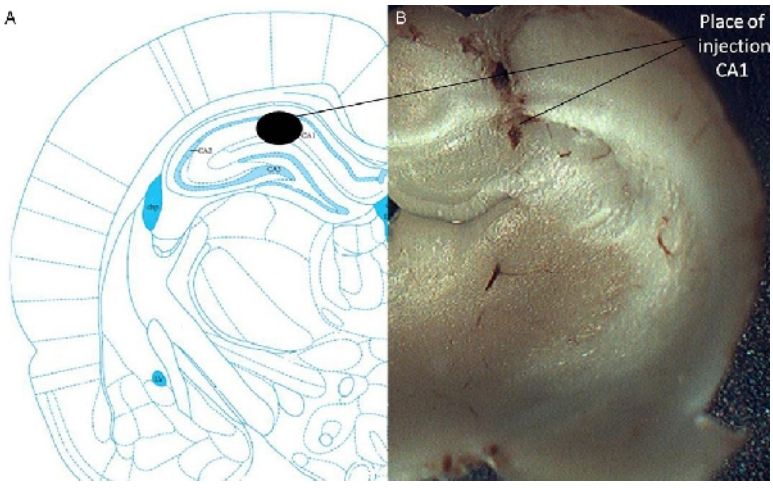

Fig. 1. (A) Verified section as taken from (Paxinos and Watson, 2007). (B) Location of the injection cannula etips in the CA1 regions of the dorsal hippocampus for all rats included in the data analyses.

Data analysis Normality of the data was evaluated by the Kolmogorov- Smirnov test. The result of this test approved the normality of the data obtained in all groups (P>0.05). The results were statistically evaluated by analysis of variance (one-way), in which the means of step-through latencies of the experimental groups on the test day were compared. Further analyses for individual between-groups comparisons were carried out using the post-hoc Tukey's test. Statistical significance levels of P value less than 0.05 were used throughout.

RESULTS

Experiment 1: The effects of ACPA on memory retrieval in rat.

In these experiments, post-training a bilateral intra-CA1 administration of ACPA (3 ng/rat) altered the step-through latency in the Step-through inhibitory avoidance task. In addition, pre-test ACPA (3 ng/rat) restored the retrieval to the control level in the test day.

Experiment 2: The effect of pre- test intra CA1 injection muscimol on the impairment of memory consolidation-induced by ACPA

In these experiments, pre-training intra-dorsal hippocampal (intra-CA1) administration of muscimol (1.5µg/rat), Furthermore, our results also indicate that impairment of memory formation induced by acute pre-training ACPA injection can be reversed by pre-test muscimol.

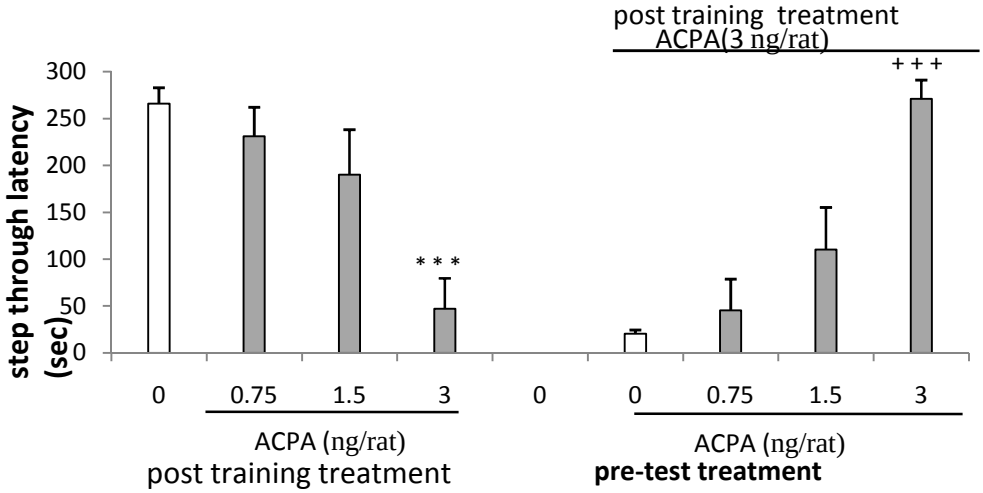

Fig. 2. The effects of post - training and pre- test administration of ACPA on memory retrieval in rat. ***P < 0.001 different from saline/saline group. +++P < 0.001different from ACPA/saline group.

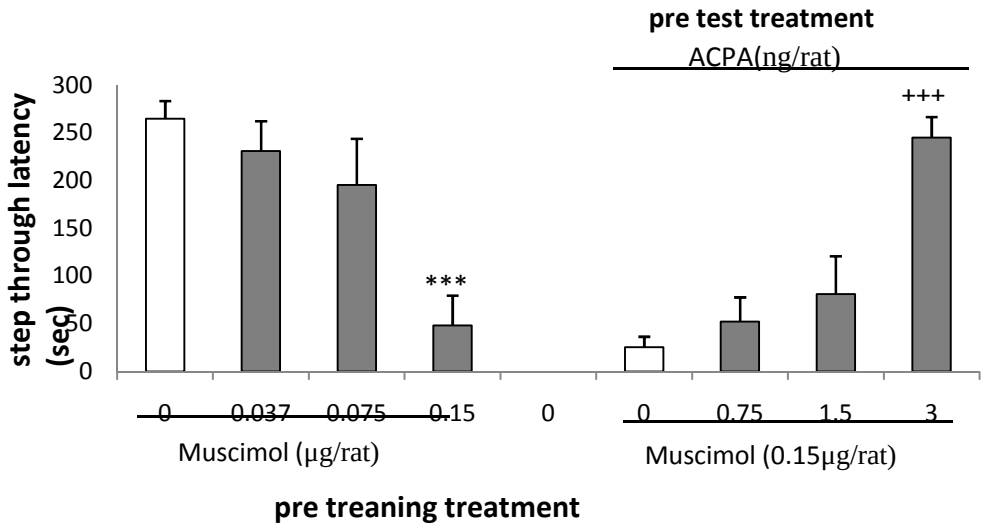

Fig. 3. The effects of pre- test administration of muscimol on memory retrieval with post- training administration of ACPA in rat. ***P < 0.001 different from saline/saline group. +++P < 0.001different from ACPA/saline group.

Experiment 3: The effect of pre- test intra CA1 injection non effective dose of muscimol and ACPA on the impairment of memory consolidation-induced by ACPA.

The pre- test injection of no effective dose of muscimol (0.037, 0.075 µg/rat) with ACPA (0.75 ng/rat) can be reversed memory consolidation-induced by ACPA but without this drugs cannot be reversed memory consolidation-induced by ACPA.

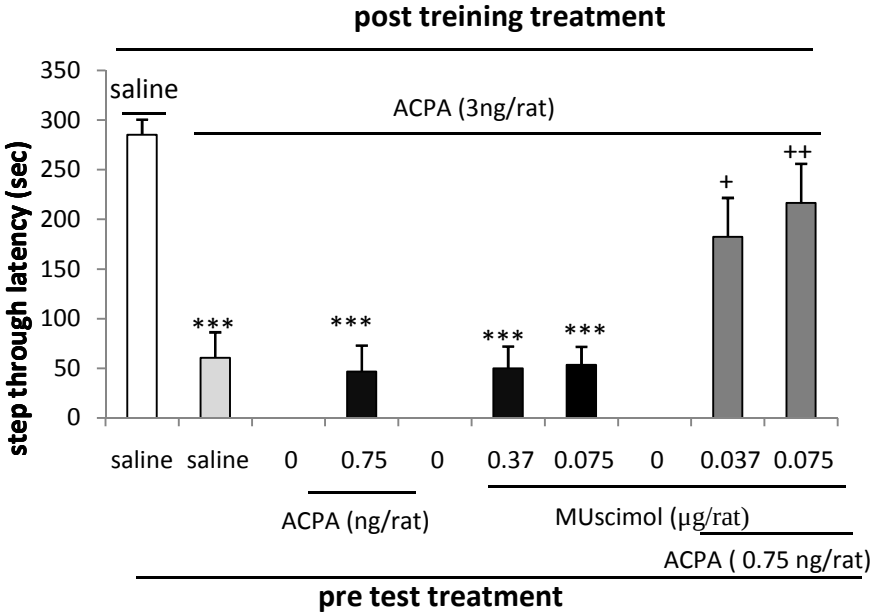

Fig. 4. The effect of pre- test intra CA1 injection non effective dose of muscimol and ACPA on the impairment of memory consolidation-induced by post-training injection of ACPA. ***P < 0.001 different from saline/saline group. ++P < 0.01, +P <0.05 different from ACPA/saline group.

DISCUSSION

In the first part of this study the effect of specific agonist canabinoid CB1 on passive avoidance memory has been studied. In the second part the effect of Gaba receptor A that is musimul, on a damage memory by ACPA has been studied. Our investigations revealed that post train injection of cannabinoid agonist , ACPA in CA1 region, 24 hours before the test caused the memory damage and amnesia.

Recent studies (Nasehi *et al.* 2009b) and other investigations have indicated that cannabinoid receptor agonists may impair (Oliveira *et al.* 2008; Nasehi *et al.* 2009b) which may be due to theCB1 recep-tor (Nasehi *et al.* 2009b). Several lines of evidence reveal that administration of cannabinoid receptor agonists block LTP in hippocampal slices (Paton *et al.* 1998). However, it has been suggested that the CB2 receptors (Weber *et al.* 2001; Nickel *et al.* 2001) and vanilloid type1receptors (Buckley *et al.* 2000) may be involved. Since, the majority of previous investigations have used knock-out animals (Bilkei-Gorzo *et al.* 2005; Varvel and Lichtman 2002) or peripheral administration of cannabinoids, it is difficult to assess the exact site of involvement. Since, CB2 and CB3 receptors are existed in the brain, the involvement of these receptor subtypes cannot be excluded (Ferrari *et al.* 1999; Varvel *et al.* 2001). The results of this study are remarkable because not only it cause not only it suggested that canabinoid agonist receptors cause the memory damage, but also it reveals this response is mediated by CB1 receptors. One of the canabinoids known functions is the long time LTP synaptic reinforcement inhibition and memory damage.

Behavioural studies have suggested direct interactions between cannabinoid and some neurotransmitter systems (Egashira *et al.* 2002; Gobbi *et al.* 2005; Malone and Taylor 1999; Hungund *et al.* 2002). This was further corroborated by findings that cannabinoid CB1 receptor agonists reduce the release of serotonergic (Molina-Holgado *et al.* 1996), the GABAergic (Garcia-Gil *et al.* 1999), the opioidergic (Vela *et al.* 1995; Vela *et al.* 1998b) and dopaminergic (Schlicker *et al.* 1996) leading to substantial and long-lasting changes in different behavioural patterns (Fernandez-Ruiz *et al.* 2000; Fernandez-Ruiz *et al.* 1999; Viveros *et al.* 2005).

Considering the importance of these nervous mediators is learning and memory, it can be concluded that ACPA could damage memory through liberation decrease in nervous mediator in hypocamp. (Gifford *et al.* 1997). On the other hand, our obtained data show that cannabinoid-induced amnesia due to post-training ACPA was fully reversed by pre-test intra-CA1 administration of the ACPA, suggesting state-dependent learning induced by the drug. Our previous studies show that drugs of abuse such as WIN55, 212-2, canabinoid receptor agonist (Zarrindast *et al.* 2011), morphine (Malekmohamadi *et al.* 2007), ethanol (Rezayof *et al.* 2008) can produce this kind of learning via the involvement of some neurotransmitter systems. Pre-training intra-dorsal hippocampal (intra-CA1) administration of the GABAergic receptor agonist, muscimol, induced memory impairment which was restored when the efect dose of the ACPA was administered 24 h later in a pre-test session. In the other word musimul could imitate ACPA effects in testing day and caused restored the retrieval to the control level in the test day.

GABA plays a controlling role on the balance of excitability and inhibitory states in the cortex, hippocam pus and the interneurons and is involved in information processing in the hippocampus (Paulsen and Moser 1998). The administration of GABAergic receptor agonists impairsmemory, while their antagonists facilitate memory storage and retrieval in inhibitory avoidance tasks (Amaral *et al.* 2007). Considerable evidence also suggests that the response of muscimol on memory could be due to its effect in the hippocampal formation (Zarrindast *et al.* 2002). However, CA1 region of the hippocampus is essential for memory formation of one-trial avoidance (Jafari-Sabet 2006), it is difficult to believe that physiological events can happen in the hippocampus without reflecting on the activity of its connections and vice versa(Zarrindast *et al.* 2002). Although when musimal is injected solely, can cause memory damage, its injection to mice affected by ACPA (specific agonist of canabinoid CB1 can improve passive avoidance memory. Considerable evidence also suggests that the time of drug administration and the site of injection of drugs may account for the discrepant effects of drugs on consolidation of memory (Pakpour *et al.* 2010)

Our results in the final section of this study indicated that ineffective amounts of musimal and ACPA which cannot rehabilitate the destroyed memory by ACPA in train day, can do so when they are used together. In support of the present results it has been reported that cannabinoid CB1 receptors play a specific role in memory extinction (Suzuki *et al.* 2004). Gamma-amino butyric acid (GABA) is the major inhibitory neurotransmitter in the brain. It is well known that the GABA-ergicsystem affects learning and memory processes (Nakagawa *et al.* 1999). Therefore stimulation of both systems can generated impartially same conditions. Consequently, ineffective amounts of them together could refine the memory which was destructed by ACPA in train day.

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