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CANNABINOIDS ALTER RECOGNITION MEMORY IN RATS

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Cannabinoids are known to attenuate learning and memory in both humans and animals. In rodents, disruptive effect of cannabinoids on memory, reversed by SR 141716, a specific CB_1 receptor antagonist, was shown in behavioral tests based on conditioning. There are no data concerning the influence of cannabinoids on recognition memory. Recently, the improvement of recognition memory in cannabinoid CB_1 receptor knock-out mice was reported. Therefore, the purpose of the present study was to determine whether a stable analogue of endogenous cannabinoid anandamide, R-(+)-methanandamide (0.25 and 2.5 mg/kg, *ip*) and a potent CB_1 receptor agonist, CP 55,940 (0.025 and 0.25 mg/kg *ip*) affect recognition memory in rats evaluated in an object recognition test, based on discrimination between the familiar and a new object presented at 1h interval. Because cannabinoids at the higher doses can produce motor inhibition, the influence of both compounds on psychomotor activity was evaluated in an open field test. CP 55,940 and R-(+)-methanandamide, at both doses given once, 15 min before the learning trial, significantly attenuated recognition memory, measured by the difference in exploration of a new object and a duplicate of the familiar object. Moreover, CP 55,940 at the higher dose significantly attenuated ambulation, and bar approaches, and at both doses also rearings, evaluated in an open field, performed immediately after an object recognition test, while R-(+)-methanandamide at both doses did not alter locomotor and exploratory activity of rats. This is the first evidence that cannabinoids impair recognition memory in rats.

Key words: *cannabinoids, recognition memory, locomotor activity, rats*

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INTRODUCTION

Marijuana (*Cannabis sativa*) remains one of the most widely abused substances in the world. Thus, modern research has focused on its potential medical employment and dangers. The cloning and subsequent mapping of G-protein-coupled receptors for cannabinoids in the brain [16, 17, 27] and discovery of endogenous cannabinergic system [10, 11, 37] led to an explosion in basic research that has attempted to integrate this putative novel neurotransmitter system in the current knowledge of the central nervous system physiology.

So far, two subtypes of cannabinoid receptors have been identified. CB_1 receptors were found primarily in the CNS, with the highest concentrations in the hippocampus, cerebellum and basal ganglia [16, 17, 27], while CB_2 receptors are expressed in the periphery and appear to be involved in modulation of the immune system [16, 28]. The neuronal localization of the CB_1 receptors is consistent with the cognition [9, 14] and motor effects [13] of cannabinergic compounds.

In humans, in addition to euphorigenic properties [1, 15], marijuana and its derivatives produce alterations in cognition and memory, anxiety, analgesia, hypothermia, stimulation of food intake, antiemetic effects, and vasorelaxation [18]. In rodents, cannabis and Δ^9-tetrahydrocannabinol (Δ^9-THC), its major psychoactive component, produce a characteristic combination of four symptoms: hypothermia, analgesia, hypoactivity and catalepsy [1, 6, 8], which are reversed by the selective CB_1 receptor antagonist SR 141716, providing a good evidence for the involvement of CB_1-related mechanisms.

There is support for the notion that cannabinoids impair cognitive processes in animals [2–5, 9, 14, 22, 23, 25, 26, 35]. Acute administration of Δ^9-THC, WIN 55,212-2 and CP 55,940, given *ip*, impaired spatial working memory in rats evaluated in an eight-arm radial maze [22]. A dose-dependent reduction of rat performance in the maze, reported following intrahippocampal application of CP 55,940, [22] may suggest that cannabinoids impair working memory independently of their motor effects. In spatial delayed alternation or delayed non-match-to-position or to-sample tasks in rats, Δ^9-THC and WIN 55,212-2 also reduced choice accuracy, whereas performance in discrimination procedures (reference memory) was not affected [9, 14, 25, 26]. The prevention of Δ^9-THC-induced deficits in radial maze choice accuracy and in delayed non-match-to-position tasks, by SR 141716 provides strong evidence that Δ^9-THC impairs working memory processes through a direct action at CB_1 receptors [14, 23, 26].

Moreover, Δ^9-THC and the metabolically stable analogue of anandamide, R-(+)-methanandamide (but not anandamide itself) exerted dose-dependent disruptive effect on learning in rats, trained in a repeated acquisition task, antagonized by SR 141716 [4].

Till now, there is only one study indicating that CB_1 receptor blockade may improve cognitive processes. This pro-cognitive effect was observed in the social recognition task in rats [36]. The above observation is in agreement with recently described enhancement of recognition memory in cannabinoid CB_1 receptor knock-out mice [29].

However, there is no data concerning the effect of cannabinoid agonists on recognition memory. Since a majority of the abovementioned experimental paradigms are based on conditioning, whereas recognition memory is a nonconditioned behavior, evaluation of the influence of cannabinoids on recognition memory would give some new indications regarding the involvement of cannabinoid system in learning and memory processes.

Thus, in the present study, the influence of CP 55,940, a potent CB_1 receptor agonist and a stable analogue of endogenous cannabinoid anandamide, R-(+)-methanandamide, on recognition memory was evaluated in an object recognition test in rats. Moreover, since cannabinoids alter motor activity of animals, their locomotor and exploratory activity was tested in an open field test.

MATERIALS and METHODS

Animals

Male Wistar rats of laboratory strain weighing 180–200 g were used after 7 days of acclimatization to the laboratory conditions. They were housed in plastic cages, four animals per cage, in a temperature-controlled room, 22 ± 1°C, under a 12 h light-dark cycle beginning at 07:00 h. Food and water were freely available.

Drugs

CP 55,940 (Tocris) and R-(+)-methanandamide (Tocris) were dissolved in 19% solution of 2-hy-

droxypropyl-β-cyclodextrin (SIGMA). Solutions for injections were prepared before each behavioral experiment and protected from light. CP 55,940 (0.025 and 0.25 mg/kg) and R-(+)-methanandamide (0.25 and 2.5 mg/kg) were given *ip* once, 15 min before T1 trial of object recognition test. At the same time the control rats received a vehicle solution only.

Behavioral tests

Object recognition test

The apparatus was a wooden box (65 × 45 × 45 cm) placed in a sound-isolated room. One bulb fastened in the upper part of the room provided a constant illumination of 40 lux at the level of the test box. Throughout the experiment no cleaning of the box was allowed, in order to saturate it with olfactory stimuli. Animals were handled and weighed each day. The procedure was similar to that described by Ennaceur and Delacour [12] and may be summarized as follows. A day before testing rats were submitted to a habituation session, whereby they were allowed to explore the apparatus for 2 min. The experimental session comprised two trials. In the first trial (T1), one object-stimulus, the sample (A), was placed near the rear wall of the box in a location equidistant from the back corners of the box. During the second trial (T2), a new object (B) was added. Here, each object was placed in a back corner. The object (A') presented during T2 was a duplicate of the sample presented in T1 (A) in order to avoid olfactory traits. From rat to rat, the role (sample or new object) and the position of the two objects during T2 was counterbalanced and randomly permuted. These precautions were taken to reduce object and place preference effects. It should be stressed that the objects apparently had no natural significance for rats and had never been associated with a reinforcement. At the beginning of each trial, rats were placed near the center of the front wall of the box, with their heads oriented in the opposite direction to the object. The respective duration of T1 and T2 was 5 and 3 min. T2 started an hour after T1 began. The basic measure was the total time spent by rats in exploring objects during T1 and T2 trials. Exploration of an object was defined as follows: directing the nose at a distance 2 cm to the object and/or touching it with the nose. Turning around or sitting on the object was not considered as exploratory behavior. From this measure, the following variables were defined: A = the time spent in exploring the sample during T1, B + A' = the time spent in exploring a duplicate of the familiar object A (A') and a new object (B) during T2. Object recognition was measured by the variable B – A'. Since B – A' may be biased by differences in overall levels of exploration, the variable B – A'/ B + A' was also computed. Moreover, the recognition index was calculated for each animal and expressed as a ratio: time B × 100/ time B + A.

Locomotor and exploratory activity

Locomotor (crossings of squares) and exploratory (rearings, bar approaches) activity was measured in an open field, which was a square white floor measuring 100 × 100 cm divided by eight lines into 25 equal squares and surrounded by a 47 cm high wall, as described earlier [38]. Four wooden bars, 20 cm high, were designed as objects of possible interest of the animals and fixed perpendicularly parallel to each other in four line crossings in the central area of the floor. The apparatus was placed in a sound-isolated room and one bulb fastened in the upper part of the room provided a constant illumination of 75 lux at the level of the test box. The animals were placed in center of open field box and crossings of squares, rearings, bar approaches and circling behavior were counted for 5 min. The open field test was carried out immediately after the object recognition test.

The object recognition and open field tests were recorded on videotape (miniDV standard) using digital camcorder. Simultaneously, the measurements during all behavioral experiments were taken manually by observers. After each session the measurements were finally counted and once again animal behavior of each rat was evaluated corresponding to the videotape data.

Statistics

The results of experiments were evaluated by one-way analysis of variance (ANOVA) followed by Dunnett test. F-ratios, degrees of freedom, and p – values are reported only for significant differences. In all comparisons between particular groups, a probability of 0.05 or less was considered significant.

RESULTS

Object recognition

The time spent in exploring object A in T1 trial (variable A) was comparable in control and in all experimental groups of rats (Tab. 1). However, exploration time of a duplicate of the familiar object A and a new object B in T2 trial (variable B + A') was significantly different between the groups. ANOVA of a control and two CP 55,940 injected groups of rats yielded $F_{2,25} = 8.67$, $p < 0.001$. A subsequent testing of the differences between the particular groups of rats with Dunnett's test showed that total time of exploration in T2 trial was significantly attenuated in both groups of rats treated with CP 55,940, as compared to control group. Object recognition memory, measured by the difference in exploration of a duplicate of the familiar object A (A') and a new object B (variable B – A') was also significantly different between the groups. ANOVA of a control and CP 55,940 injected groups of rats yielded $F_{2,25} = 4.50$, $p < 0.02$ and ANOVA of a control and both R-(+)-methanandamide-treated groups of rats yielded $F_{2,25} = 7.47$, $p < 0.002$. Further *post-hoc* comparisons made with Dunnett's test revealed significant attenuation of recognition memory in all cannabinoid-treated groups of rats. Moreover, the recognition index calculated for each animal and expressed as a ratio: time B × 100/time A' + time B was significantly different between the groups (Fig. 1). ANOVA for one control and both CP 55, 940 or both R-(+)-methanandamide-treated

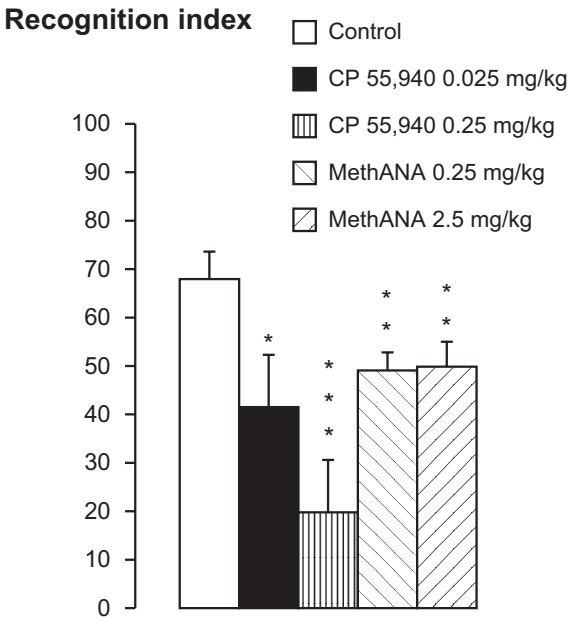

Fig. 1. Effect of CP 55,940 and R-(+)-methanandamide given *ip* once, 15 min before T1 trial of object recognition test, on recognition index. Columns represent means ± SEM of the values obtained from 8 controls and 10 rats of each experimental group. * $p < 0.05$, ** $p < 0.02$, *** $p < 0.005$ *vs.* control group (ANOVA and Dunnett's test)

Table 1. Effect of R-(+)-methanandamide and of CP 55,940 on acquisition evaluated in an "object recognition" test

Variables (s)	Treatment				
	Control	0.025 mg/kg CP 55,940	0.25 mg/kg CP 55,940	0.25 mg/kg R-(+)-methanandamide	2.5 mg/kg R-(+)-methanandamide
B – A'	10.250	3.538*	–2.333**	–2.384***	–1.153***
	(5.924)	(4.305)	(3.431)	(2.197)	(3.725)
A	17.750	25.000	13.750	19.615	23.384
	(2.169)	(3.919)	(6.112)	(4.418)	(5.457)
B + A'	35.750	19.000*	11.666***	28.230	32.538
	(5.942)	(4.006)	(4.718)	(5.372)	(5.035)
B – A'/B + A'	0.424	0.429	0.342	0.224	0.355
	(0.101)	(0.114)	(0.113)	(0.046)	(0.090)

Table presents means ± SEM (in parentheses) of the values obtained from 8 controls and 10 rats of each experimental group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$ *vs.* control group of rats (ANOVA and Dunnett's test)

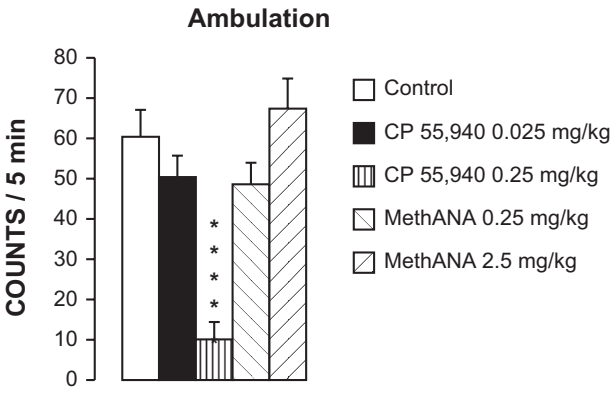

Fig. 2. Effect of CP 55,940 and R-(+)-methanandamide given *ip* once, 15 min before T1 trial of object recognition test on ambulation (measured by square crossings) evaluated in an open field performed immediately after object recognition test. Columns represent means ± SEM of the values obtained from 8 controls and 10 rats of each experimental group. **** $p < 0.001$ *vs.* control group (ANOVA and Dunnett's test)

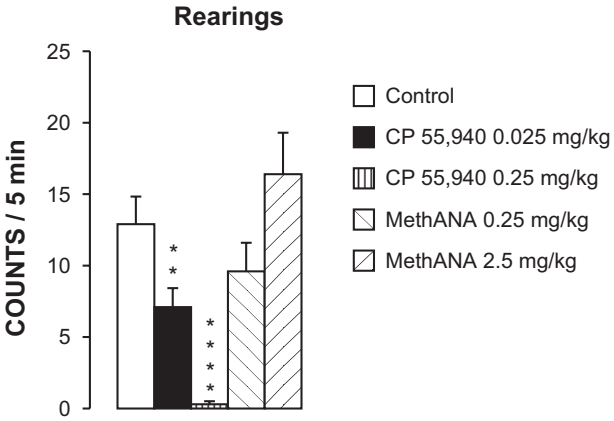

Fig. 3. Effect of CP 55,940 and R-(+)-methanandamide given *ip* once, 15 min before T1 trial of object recognition test, on rearings evaluated in an open field performed immediately after object recognition test. Columns represent means ± SEM of the values obtained from 8 controls and 10 rats of each experimental group. ** $p < 0.02$, **** $p < 0.001$ *vs.* control group (ANOVA and Dunnett's test)

groups of rats yielded $F_{2,25} = 5.62$, $p < 0.01$ and $F_{2,25} = 4.47$, $p < 0.02$, respectively. A subsequent comparison between particular groups of rats with Dunnett's test revealed significant depression of recognition index in all groups injected with cannabinoids in comparison with the control group, that was the most pronounced after the higher dose of CP 55,940. In control animals, the recognition index was higher than 50% (time B was superior to time A') indicating that they have remembered the familiar object, while in all groups of rats injected

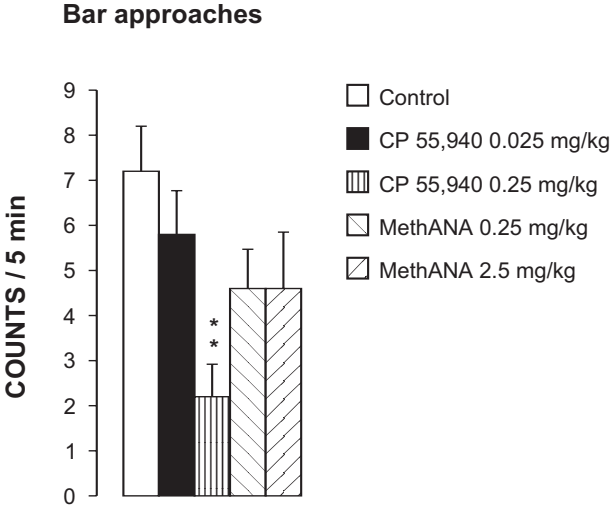

Fig. 4. Effect of CP 55,940 and R-(+)-methanandamide given *ip* once, 15 min before T1 trial of object recognition test, on bar approaches evaluated in an open field performed immediately after object recognition test. Columns represent means ± SEM of the values obtained from 8 controls and 10 rats of each experimental group. ** $p < 0.02$ *vs.* control group (ANOVA and Dunnett's test)

with cannabinoids recognition index was below 50% (time B and time A' were comparable), which indicates that the animals did not remember the familiar object.

Locomotor activity

Locomotor activity measured as a number of square crossings was significantly different between the particular groups (Fig. 2). ANOVA of a control and both CP 55,940 – treated groups of rats yielded $F_{2,25} = 23.60$, $p < 0.00001$. *Post-hoc* comparison made with Dunnett's test revealed significant attenuation of locomotor activity in rats treated with the higher dose of CP 55, 940. Also exploratory activity measured by rearings (Fig. 3) and bar approaches (Fig. 4) was different between the groups of rats. ANOVA of a control and both CP 55,940-treated groups of rats yielded $F_{2,25} = 24.85$, $p < 0.00001$, and $F_{2,25} = 5.94$, $p < 0.01$, respectively. A subsequent evaluation made by Dunnett's test indicated significant attenuation of rearings in both groups of rats treated with CP 55,940 and significant decrease in number of bar approaches only after the higher dose of this compound. Moreover, CP 55,940 application evoked circling behavior observed during T1 and T2 trial in object recognition test, as well as in open field in 30% and

in 100% of rats injected with a lower and a higher dose, respectively.

DISCUSSION

This is the first evidence that cannabinoids exert disruptive effect on recognition memory in rats. Memory was assessed by using the two-trial object recognition test as previously described by Ennaceur and Delacour [12], based on discrimination between the familiar and a new object presented at 1 h interval. While control rats significantly longer explored a new object than the familiar one, the animals injected with low and high doses of both cannabinoids explored both objects similarly. Thus, the control animals injected with a vehicle had high recognition index, while in animals, injected 15 min before training session (T1) with cannabinoids, recognition index declined below 50% which indicates their inability to recognize the familiar object.

Because cannabinoids, at higher doses, are known to alter motor functions by inhibition of locomotor activity [8, 13, 19–21, 31, 34] and development of circling behavior [32, 33], a low and a high dose of both cannabinoids was used in the present study. Since ambulation, measured by square crossings, evaluated in an open field immediately after an object recognition test, was significantly attenuated only in rats injected with the higher dose of CP 55,940, which also evoked circling behavior, we believe that the reduction of time spent on exploration was not due to a decrease in locomotor activity. Moreover, it was observed that CP 55,940, especially at the higher dose, attenuated exploratory activity of rats measured by number of rearings and bar approaches. Although the total time of exploration of both objects (B + A') in T2 trial was significantly attenuated after CP 55,940 (but not after R-(+)-methanandamide) application, the attenuation of recognition memory caused by both cannabinoids was comparable. This may indicate that the difference observed between the control and experimental groups was due to differences in memory retention.

Our results are consistent with the results obtained in CB_1 receptor knock-out mice and with CB_1 receptor blockade in rats. On the contrary to our finding with CB_1 receptor activation, lack of CB_1 receptors in CB_1 receptor knock-out mice improved retention of learned information till 48 h in object recognition test [29]. Also Terranova et al. [36] have reported that CB_1 receptor antagonist SR 141716 [30] dose dependently improved social recognition in a 120-min inter-trial paradigm, in which control rats normally failed to recognize the same juvenile.

There are a lot of data indicating that cannabinoids impair learning and memory in rodents [2–5, 9, 14, 22, 23, 25, 26, 35]. Acute administration of Δ^9-THC, WIN 55,212-2 and CP 55,940, given *ip*, impaired spatial working memory in rats evaluated in an eight-arm radial maze [22]. Moreover, a dose-dependent reduction of maze performance, but not maze completion time was reported following intrahippocampal application of CP 55,940 [22]. Similarly to our findings, these results suggest that cannabinoids impair working memory independently of their motor effects. In spatial delayed alternation or delayed non-match-to-position or to-sample tasks in rats, Δ^9-THC and WIN 55,212-2 also reduced choice accuracy, whereas performance in discrimination procedures (reference memory) was not affected [9, 14, 25, 26]. The prevention of Δ^9-THC-induced deficits in radial-maze choice accuracy and in delayed non-match-to-position tasks, by SR 141716 provides strong evidence that Δ^9-THC impairs working memory processes through a direct action at CB_1 receptors [14, 23, 26].

On the contrary to Δ^9-THC, anandamide did not alter working memory processes evaluated by choice accuracy in a delayed non-match-to-sample in mice [14] and in eight-arm radial maze task in rats [22]. However, in mice, anandamide (3 to 6 mg/kg, *ip*) administered immediately after training reduced the retention performance 24 h later, suggesting an action during the memory consolidation phase [5]. Moreover, a reduction of correct choices in a delayed non-match-to position task, sensitive to SR 141716 pretreatment, was observed in rats injected with anandamide (0.5 to 4.0 mg/kg, after pretreatment with the protease inhibitor PMSF, to prevent its metabolic degradation), whereas reference memory was not altered [7, 25, 26]. Moreover, Δ^9-THC and the metabolically stable analogue of anandamide, R-(+)-methanandamide (but not anandamide itself) exerted dose-dependent disruptive effect on learning in rats, antagonized by SR 141716 [4]. The impairment of recognition memory, observed in our study, was comparable in CP 55,940- or R-(+)-methanandamide-treated rats, although the latter one was applied at ten-fold higher doses than CP 55,940.

However, the majority of the mentioned tasks are not purely one-trial since they involve the learning of a rule (matching, or non-matching to sample) through the repetition of stimulus or response reward associations. Alterations of performances by drugs or brain lesions may be shown either by effects on the one-trial component or on the learning of a rule, or even both. Compared to most other models, in one-trial object recognition test used in our study, the arousal and motivational states are much more similar to those under which the human memory is usually measured.

The present results confirmed the hypothesis created on the basis of the experiments performed on CB_1 receptor knock-out mice [24, 29] that an endogenous cannabinoid tonus is present under physiological conditions and is involved in the modulation of memory.

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