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Short communication

Cannabinoid CB_1 receptor is dispensable for memory extinction in an appetitively-motivated learning task

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Abstract

The interaction of the cannabinoid CB_1 receptor with its endogenous ligands plays an essential role in extinction of aversive memories (Marsicano, G., Wotjak, C.T., Azad, S.C., Bisogno, T., Rammes, G., Cascio, M.G., Hermann, H., Tang, J., Hofmann, C., Zieglgansberger, W., Di, M., V, Lutz, B., 2002. The endogenous cannabinoid system controls extinction of aversive memories. Nature 418, 530–534). The present study tested the generality of this observation in respect to positively-reinforced memories. To this end, male cannabinoid CB_1 receptor deficient mice ($CB_1R^{-/-}$) and their wild-type littermate controls ($CB_1R^{+/+}$) were trained in an appetitively-motivated operant conditioning task, in which food-deprived animals received a food reward on nose-poking into an illuminated hole. During training, $CB_1R^{-/-}$ turned out to be less motivated to participate in the task. After further restriction of daily food consumption, however, $CB_1R^{-/-}$ reached the same level of performance as $CB_1R^{+/+}$ as far as number of correct responses and errors of omission are concerned. The accuracy of performance served as a measure for the memory of the light-reward association and was stable at similarly high levels over a retention period of 9 days without additional training (97.6±0.5% vs. 97.0±0.9% correct responses). During subsequent extinction training, the positive reinforcement was omitted. As a consequence, both $CB_1R^{-/-}$ and $CB_1R^{+/+}$ showed a similar decline in accuracy of performance and total number of correct responses, accompanied by an increase in errors of omission. These data demonstrate that the cannabinoid CB_1 receptor is not essential for extinction of the stimulus–response association in an appetitively-motivated learning task.

Keywords: CB_1; Endocannabinoid; Conditioning; Motivation; Food consumption; Knock-out

1. Introduction

Whereas pharmacological effects of cannabinoids on learning and memory have been well described (for reviews see Ameri, 1999; Lichtman et al., 2002; Sullivan, 2000; Castellano et al., 2003), the contribution of the endogenous cannabinoid system to these processes has remained enigmatic. Only recently, it has become evident that the role of endocannabinoids in cognition seems to predominantly relate to the retention of recognition memory (Reibaud et al., 1999; Terranova et al., 1996) and reference spatial memory (Lichtman, 2000; Wolff and Leander, 2003), with little consequences on working spatial memory (Hampson and Deadwyler, 2000; Ledent et al., 1999; Nava et al., 2001; Varvel and Lichtman, 2002). For instance, blockade of the cannabinoid CB_1 receptor with a specific antagonist prolonged retention of juvenile recognition in adult mice and rats, restored juvenile recognition in aged mice and rats and disrupted the amnesic consequences of retroactive interference (Terranova et al., 1996). Accordingly, cannabinoid CB_1 receptor deficient mice showed prolonged recognition of a familiar object as compared to wild-type littermate controls (Reibaud et al., 1999; Maccarrone et al., 2002).

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Pharmacological blockade of the cannabinoid CB_1 receptor improved memory performance in an appetitively-motivated spatial learning task, if a cannabinoid CB_1 receptor antagonist was administered before or immediately after training (Lichtman, 2000; Wolff and Leander, 2003), suggesting a role of the endogenous cannabinoid system also in memory acquisition. The situation appeared to be different in aversively-motivated learning tasks. As assessed in cannabinoid CB_1 receptor deficient mice, the cannabinoid CB_1 receptor seems to be dispensable for both acquisition and consolidation of fear memories in a fear conditioning paradigm and spatial memory in a water maze (Marsicano et al., 2002; Varvel and Lichtman, 2002). In both tasks, the cannabinoid CB_1 receptor seems to play a specific role in memory extinction (Marsicano et al., 2002; Varvel and Lichtman, 2002; Suzuki et al., 2004). So far, studies on molecular correlates of extinction have largely concentrated on aversive memories (for review see Myers and Davis, 2002). Little is known as to whether or not extinction of aversive and extinction of positive memories involve similar cellular and molecular processes. Therefore, the present study investigated memory extinction in an appetitively-motivated operant conditioning task in cannabinoid CB_1 receptor deficient mice.

2. Materials and methods

2.1. Animals

At an age of 11–14 weeks, adult male mice deficient for the cannabinoid CB_1 receptor ($CB_1R^{-/-}$, n=10; Marsicano et al., 2002; F6 generation backcrossed to C57BL/6NCrl, Charles River, Bad Sulzfeld, Germany) and littermate controls ($CB_1R^{+/+}$, n=12) were housed individually in IVC-racks under standard laboratory conditions with food and water ad libitum and a 12 h:12 h light–dark cycle (lights on: 07:00 h). After 7 days of recording of ad libitum food consumption and body weights, mice were food restricted. The amount of food needed to keep 85% of ad libitum feeding body weight was calculated individually for each animal. During subsequent training, food was given approximately 1 h after the training session. Experiments were approved by the Committee on Animal Health and Care of the local governmental body.

2.2. Operant conditioning set-up

Animals had to attend to a curved wall with 5 holes (2 cm in diameter, 3 cm deep, 1.5 cm above floor level) within an operant conditioning chamber (TSE, Bad Homburg, Germany; van Gaalen et al., 2003). Each hole was equipped with a photocell beam crossing the hole's entrance horizontally, a yellow LED at the rear of the hole and a food dispenser. The operant conditioning chambers were located in isolation cubicles and could be illuminated by a white house light (30 lx) mounted to the roof of the chamber. Stimulus presentation during a trial, data acquisition and storage were controlled by a PC (software package OBS, V1.56, TSE).

A session consisted of 60 trials with an inter-trial interval of 20 s. A trial started with illumination of one of the five holes selected in pseudorandom order but equally distributed across the five holes in each session. The illumination persisted for 8 s. Mice received a 20 mg dustless food pellet (BioServ, Frenchtown, NJ, USA), if they nose-poked into the illuminated hole within a limited hold of 10 s (correct responding). A nose-poke into one of the four non-illuminated holes (incorrect responding) or the non-initiation of a nose-poke within the limited hold (error of omission) resulted in a time out period (5 s), signaled by house light on. Premature responses during the last second of the inter-trial interval prolonged this interval for another second in order to prevent stimulus presentation while an animal was not able to pay attention. A session ended after completion of all 60 trials or after 45 min had elapsed, whichever occurred first.

2.3. Experimental protocol

Sessions were performed between 09:00 h and 12:00 h. In the beginning of the experiment, mice were habituated to the test chambers by manually placing 2 pellets into each hole until all mice ate all pellets, followed by an autoshaping phase of 20 trials/session. After completion of autoshaping (10 sessions were needed until all mice completed 20 trials/session), acquisition training phase 1 (*A1*) started, during which both $CB_1R^{-/-}$ and $CB_1R^{+/+}$ were kept at 85% body weight and received 12 training sessions distributed over 17 days. Because errors of omission were still significantly higher in $CB_1R^{-/-}$ than in $CB_1R^{+/+}$ at the end of *A1*, $CB_1R^{-/-}$ were further reduced to 80% body weight, whereas $CB_1R^{+/+}$ remained at 85% body weight during acquisition training phase 2 (*A2*). After mice of both genotypes had reached the criterion [3 consecutive days of stable and equivalent performance in both groups concerning accuracy (%correct responses) and motivation (errors of omission)], daily training sessions were discontinued for 9 days, followed by a retention session (*R*) in order to assess long-term retention of the performance level. One day after *R*, the feeders were emptied and 9 extinction sessions without food reinforcement (*E*) were carried out, distributed over 11 days.

2.4. Parameters measured

The software automatically recorded correct responses (nose-poke responses into the illuminated hole within the limited hold), incorrect responses (nose-poke responses into a non-illuminated hole within the limited hold), inter-trial interval responses ("premature" responses during the inter-

trial interval), number of trials and duration of the session. The following indicators of behavioral performance were calculated from these data:

- *% Correct responses* were calculated as the ratio of the number of correct responses and the sum of the number of correct and incorrect responses, multiplied by 100. This parameter reflects the accuracy of performance, i.e., how well the animal has learned the task.
- *Errors of omission* were calculated as the difference between the number of trials and the sum of correct and incorrect responses. This parameter primarily reflects the motivation of the animal to participate in the task, but might also be confounded by differences in motor activity.
- *Total responding* was calculated as the sum of correct responses, incorrect responses and inter-trial interval responses.
- *Response bias* was calculated as the difference of the total responding to the left two holes and the total responding to the right two holes, divided by the sum of total responding to the left two and the right two holes, expressed as an absolute value. This parameter reflects a response bias to one side of the 5 stimulus holes. In case of no side bias, the response bias is 0. During acquisition training, response bias is an additional control parameter reflecting whether an animal sufficiently learns the task to pay equal attention to all possible locations of stimulus presentation.

2.5. Statistics

Data were expressed as mean±S.E.M. and analyzed by 2-way analysis of variance (ANOVA; *Genotype*, *Session*) for repeated measures (*Session*) separately for acquisition phase 1 (*A1*), acquisition phase 2 (*A2*) and the extinction phase (*E*). Post-hoc analyses were performed by Newman–Keuls test. Data of the retention session (*R*) were analyzed by unpaired *t*-test. Statistical significance was accepted if $P<0.05$.

3. Results

As shown in Fig. 1A, $CB_1R^{-/-}$ displayed more errors of omission than $CB_1R^{+/+}$ during acquisition phase *A1* [Factor *Genotype*: $F(1,20)=7.5$, $P=0.012$; *Genotype*×*Session* interaction: $F(11,220)=0.6$, $P=0.850$], indicating that the mutants were less motivated to forage for food. Accordingly, a further reduction of the body weight in $CB_1R^{-/-}$ during acquisition phase *A2* equalized the performance of the two genotypes towards the end of training [Factor *Genotype*: $F(1,20)=6.8$, $P=0.017$; *Genotype*×*Session* interaction: $F(10,200)=1.9$, $P=0.047$], as post-hoc analyses failed to detect significant differences between $CB_1R^{-/-}$ and $CB_1R^{+/+}$ during the last 5 training sessions. An additional ANOVA performed for the last 5 training sessions confirmed the latter finding as no significant effects of the two main factors and their interaction could be obtained (statistics not shown).

An altered motivation and/or ability of $CB_1R^{-/-}$ to participate in the task was also reflected by the number of total responses, which largely resembled the genotype differences observed for the errors of omission during *A1* [Factor *Genotype*: $F(1,20)=10.0$, $P=0.005$] and *A2* [Factor *Genotype*: $F(1,20)=4.7$, $P=0.042$; *Genotype*×*Session* interaction: $F(10,200)=0.8$, $P=0.606$; Fig. 1B]. Accordingly, also the absolute number of correct responses was different between the two genotypes during *A1* [Factor *Genotype*: $F(1,20)=7.2$, $P=0.014$] and *A2* [Factor *Genotype*: $F(1,20)=8.6$, $P=0.008$; *Genotype*×*Session* interaction: $F(10,200)=1.8$, $P=0.065$]. These differences disappeared towards the end of training (Fig. 1C). Importantly, there was a general increase in the number of correct responses over the course of training [*A1*, Factor *Session*: $F(11,220)=23.7$, $P<0.0001$; *A2*, Factor *Session*: $F(10,200)=5.2$, $P<0.0001$], indicating that both $CB_1R^{+/+}$ and $CB_1R^{-/-}$ had learned the task. This conclusion is supported by the number of incorrect responses that decreased over the course of training [*A1*, Factor *Session*: $F(11,220)=9.8$, $P<0.0001$; *A2*, Factor *Session*: $F(10,200)=1.6$, $P=0.117$; no significant *Genotype*×*Session* interactions; Fig. 1D].

The measures of accuracy (% correct responses) revealed a general improvement in performance during *A1* [Factor *Session*: $F(11,220)=17.1$, $P<0.0001$] and *A2* [Factor *Session*: $F(10,200)=2.1$, $P=0.026$] that was independent of the genotype (no significant *Genotype*×*Session* interactions; Fig. 1E). $CB_1R^{-/-}$ performed less accurate than $CB_1R^{+/+}$ during *A2* [Factor *Genotype*: $F(1,20)=11.2$, $P=0.003$]. This difference, however, appears to be of minor biological significance as both genotypes reached accuracy levels between 93% and 100% (94.7±0.8% vs. 97.1±0.9% correct responses; inset to Fig. 1E).

Despite re-appearance of genotype differences in motivation [errors of omission: $t(20)=3.1$, $P=0.006$, Fig. 1A; number of correct responses: $t(20)=2.8$, $P=0.011$, Fig. 1C], $CB_1R^{-/-}$ showed the same high accuracy of performance as $CB_1R^{+/+}$ during assessment of memory retention (*R*; 97.6±0.5% vs. 97.0±0.9%; $t(20)=0.5$; $P=0.644$, Fig. 1E). Omission of the food reward during extinction training *E* led to a significant reduction in accuracy [Factor *Session*: $F(8,160)=8.7$, $P<0.001$] that was independent of the genotype of the animals [Factor *Genotype*: $F(1,20)=3.3$, $P=0.086$; *Genotype*×*Session* interaction: $F(8,160)=1.5$, $P=0.152$; Fig. 1E]. Moreover, extinction training was accompanied by an increase in errors of omission [Factor *Session*: $F(8,160)=135.4$, $P<0.001$; Fig. 1A] and decreases in the number of total responses [Factor *Session*: $F(8,160)=50.6$, $P<0.001$; Fig. 1B] and correct responses [Factor *Session*: $F(8,160)=175.8$, $P<0.001$; Fig. 1C]. Significant *Genotype* differences [errors of omission: $F(1,20)=16.2$, $P<0.001$; total responses: $F(1,20)=5.5$,

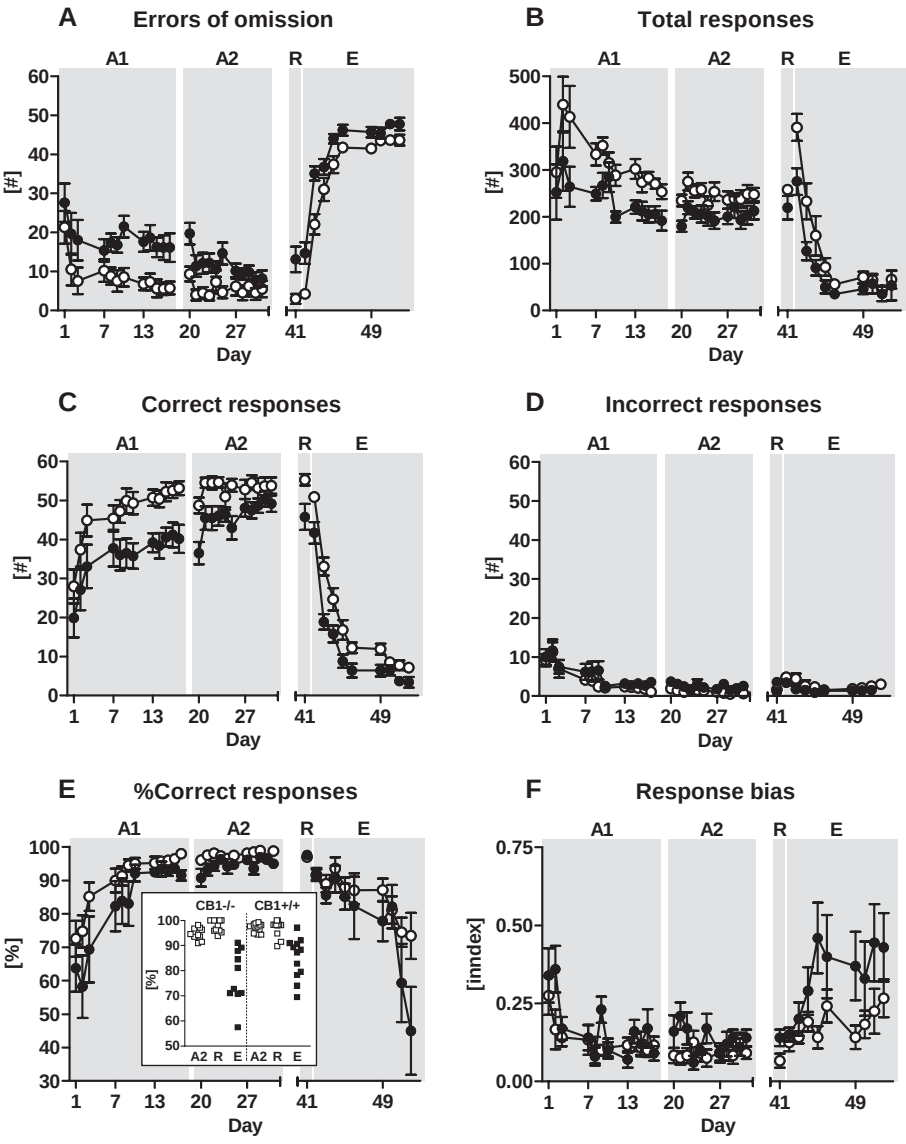

Fig. 1. Cannabinoid CB_1 receptor deficient mice show normal extinction in an operant conditioning task. $CB_1R^{-/-}$ (filled circles, n=10) and $CB_1R^{+/+}$ littermate controls (open circles, n=12) were food restricted in order to motivate them to participate in the operant conditioning task. In this task, mice had to learn to nose-poke into an illuminated hole that was pseudorandomly chosen out of 5 holes. During acquisition training phase 1 (*A1*), the body weight of the animals was reduced to 85%. During acquisition training phase 2 (*A2*), the body weight of $CB_1R^{-/-}$ was further reduced to 80% in order to improve their performance. After mice of both genotypes had reached the training criterion, daily training sessions were discontinued for 9 days, followed by a retention session (*R*) and 9 extinction sessions (*E*), the latter without food reinforcement. The following parameters were considered in order to assess the involvement of the cannabinoid CB_1 receptor in memory acquisition and extinction in the appetitively motivated learning task: (A) number of errors of omission, (B) number of total responses, (C) number of correct responses, (D) number of incorrect responses, (E) number of correct responses normalized to the sum of correct and incorrect responses (% correct responses) and (F) response bias. The errors of omission primarily reflect the motivation of the animals to participate in the task. % Correct responses describe the accuracy of performance and serve as a measure for the memory of the stimulus–response association. The inset in panel E depicts the mean accuracy of performance of each individual animal displayed during *A2* (acquisition training phase 2, open squares), *R* (retention session, open squares) and *E* (extinction sessions, filled squares). Mean±S.E.M. per session with each session consisting of a maximum of 60 trials. For the results of statistical analyses see the Results section.

P=0.029; correct responses: $F(1,20)$=16.6, P<0.001] and *Genotype*×*Session* interactions of the last three parameters [errors of omission: $F(8,160)$=2.9, P=0.004; total responses: $F(8,160)$=2.4, P=0.016; correct responses: $F(8,160)$=3.3, P=0.001] relate to the fact that extinction of performance was more pronounced in $CB_1R^{-/-}$ than in $CB_1R^{+/+}$, likely because of genotype differences in motivation.

The number of incorrect choices remained fairly unchanged during extinction training compared to acquisition phase *A2* and retention session *R* (statistics not shown; Fig. 1D). In contrast, both $CB_1R^{-/-}$ and $CB_1R^{+/+}$ showed an increase in response bias over the course of extinction training [Factor *Session*: $F(8,152)$=2.4, P=0.016] that was more pronounced in the mutants [Factor *Genotype*:

$F(1,19)=6.8$, $P=0.017$; Fig. 1F], also likely because of genotype differences in motivation.

4. Discussion

The present study investigated the role of the cannabinoid CB_1 receptor for memory extinction in an appetitively-motivated learning task. Reduction of the body weight to 85% sufficiently motivated $CB_1R^{+/+}$ controls, but not $CB_1R^{-/-}$, to participate in the task. To minimize potentially confounding influences of differences in motivation on extinction learning, the food supply was further reduced to 80% in $CB_1R^{-/-}$. Under these conditions, $CB_1R^{-/-}$ and $CB_1R^{+/+}$ showed comparable levels of performance towards the end of training, indicating that differences in motivation rather than motor capabilities account for the genotype differences during food restriction to 85%. The necessity of stronger food restriction in $CB_1R^{-/-}$ is in line with the known role of the endocannabinoid system in the regulation of energy balance and its involvement in central mechanisms controlling appetite and food reward (Cota et al., 2003; Di Marzo et al., 2001; Freedland et al., 2000; Kirkham and Williams, 2001; De Vry et al., 2004).

Compared to $CB_1R^{+/+}$, $CB_1R^{-/-}$ showed a significant delay in the increase in accuracy of performance that might be partially explained by the differences in motivation. Towards the end of training and during the retention session, however, $CB_1R^{-/-}$ showed the same high accuracy of performance as $CB_1R^{+/+}$. We conclude from these observations that (1) $CB_1R^{-/-}$ are able to form a stimulus–response association in an operant conditioning task with positive reinforcement and (2) the cannabinoid CB_1 receptor does not affect retention and recall of this memory.

Continuation of training without food reinforcement led to extinction of memory performance, characterized by a drop in the accuracy of performance and the absolute number of correct responses in both $CB_1R^{-/-}$ and $CB_1R^{+/+}$. These data indicate that mutants and controls learned to the same extent that the light stimulus is not followed by the positive reinforcement anymore. Omission of reinforcement led to a transient increase in the number of total responding that was more pronounced in $CB_1R^{+/+}$ than in $CB_1R^{-/-}$. This increase primarily relates to an increase in inter-trial interval responding (data not shown), as the number of correct and incorrect responses decreased or were only negligibly altered. It most likely reflects the search for alternative strategies aimed at obtaining the food reward during extinction training. The fact that $CB_1R^{-/-}$ mice displayed less effort in this respect and developed a response bias might relate to their altered motivation to forage for food and/or to different motor behavior.

Taken together, our data demonstrate that the cannabinoid CB_1 receptor is not critically involved in extinction of the stimulus–response association in this appetitively-motivated learning task. To the best of our knowledge, this is one of the first studies indicating that different cellular and/or molecular mechanisms may underlie the extinction of positive and aversive memories with the cannabinoid CB_1 receptor playing an important role primarily in extinction of aversively-motivated memories (Marsicano et al., 2002; Varvel and Lichtman, 2002; Suzuki et al., 2004). Further studies are needed to clarify whether this is related to the emotional valence of the stimulus or other aspects of procedural differences of commonly used aversively- and appetitively-motivated learning tasks.

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