Mol Neurobiol (2007) 36:92–101
DOI 10.1007/s12035-007-8004-x

The Endocannabinoid System and Extinction Learning

Beat Lutz

Received: 2 February 2007 / Accepted: 20 July 2007 / Published online: 17 August 2007

Abstract The endocannabinoid system has emerged as a versatile neuromodulatory system, implicated in a plethora of physiological and pathophysiological processes. Cannabinoid receptor type 1 (CB1 receptor) and endocannabinoids are widely distributed in the brain. Their roles in learning and memory have been well documented, using rodents in various memory tests. Depending on the test, the endocannabinoid system is required in the acquisition and/or extinction of memory. In particular, the activation of CB1 receptor-mediated signaling is centrally involved in the facilitation of behavioral adaptation after the acquisition of aversive memories. As several human psychiatric disorders, such as phobia, generalized anxiety disorders, and posttraumatic stress disorder (PTSD) appear to involve aberrant memory processing and impaired adaptation to changed environmental conditions, the hope has been fuelled that the endocannabinoid system might be a valuable therapeutic target for the treatment of these disorders. This review summarizes the current data on the role of the endocannabinoid system in the modulation of extinction learning.

Keywords Endocannabinoids · Cannabinoid receptor · THC · Extinction · Habituation · Anxiety · Posttraumatic stress disorder · Phobia · Rodent · Fear conditioning

B. Lutz (✉)
Department of Physiological Chemistry,
Johannes Gutenberg-University Mainz,
Duesbergweg 6,
D-55099 Mainz, Germany
e-mail: blutz@uni-mainz.de

Introduction

Endocannabinoids are lipid-signaling molecules belonging to the class of eicosanoides. During the last 15 years, remarkable insights into the roles of this signaling system in numerous physiological and pathophysiological processes have been gained [1–9]. A vast literature exists regarding the memory-impairing effects in animals and humans after treatment with Δ^9-tetrahydrocannabinol (THC), the major psychoactive component in extracts from *Cannabis sativa* [10–13]. Recent investigations gave new insights into the impairing effect of THC in hippocampal-dependent memory. THC treatment in rat leads to a decrease in the power of hippocampal oscillatory processes, suggesting that THC interferes with the temporal synchrony of neuronal networks [14]. The constituents of the endocannabinoid system (ECS), consisting of cannabinoid receptors, endocannabinoids, and enzymatic machinery for the synthesis and degradation of endocannabinoids, are abundantly expressed in all the major brain regions which are involved in learning and memory, including hippocampus, amygdala, cerebral cortex, striatum, and cerebellum [15–18]. The discovery of the ECS asked for clarifying the endogenous roles of this novel neuromodulatory system in memory processing. Detailed insight has been obtained using mice with genetic alterations in the ECS. Particularly fruitful has been the analysis of mutant mice lacking the cannabinoid receptor type 1 (CB1 receptor) [19–23], as CB1 receptors are involved in several processes modulating neuronal activities [24, 25], while the cannabinoid receptor type 2 (CB2 receptor) is mainly involved in immune responses [26]. Additional understanding was gained by the analysis of mice deficient for the anandamide degrading enzyme fatty acid amide hydrolase (FAAH) [27], and the transient receptor potential vanilloid type 1 (TRPV1) ion channel

[28], which is activated by the endocannabinoid anandamide. Pharmacological treatments of mice and rats with antagonists or inhibitors targeting constituents of the ECS have also been instrumental in these investigations [3], in particular, CB1 receptor antagonists [29–31], inhibitors for FAAH [32], and inhibitors for the endocannabinoid membrane transporter [33–35].

Endocannabinoids and the Acquisition of Memory

A broad spectrum of behavioral assays has been employed, each of them addressing various phases of memory processing (i.e., acquisition/consolidation and extinction/reconsolidation) and several different types of memories (i.e., declarative/spatial, emotional, and operant/habitual learning) [36]. Since the treatment of humans and rodents with exogenous cannabinoid receptor agonist mostly leads to impairments in the acquisition of memory, it was evident to ask whether or not blockade of CB1 receptors would enhance memory acquisition. Indeed, CB1 receptor-deficient mice display increased memory performance in certain behavioral tasks, specifically in object recognition [37, 38], active avoidance [39], and partner recognition [40]. Remarkably, Bilkei-Gorzo et al. [40] showed that the enhanced memory performance in CB1-deficient mice is age-dependent, being superior in young age, but inferior in old age as compared to wild-type control mice. This age-dependent decline in performance is possibly caused by neurodegenerative processes in the hippocampus, as it is proposed that the ECS contains a general neuroprotective function in the brain [41, 42]. Studies using the CB1 antagonist SR141716 (also called rimonabant) showed increased memory performance in juvenile recognition [43], and radial maze [44, 45]. However, memory-enhancing effects were not observed in several operant paradigms [46–48], and in trace eye-blink conditioning, which is known to depend on hippocampal function [49]. Unexpectedly, FAAH-deficient mice also display an accelerated acquisition in the water maze task, although the animals contain much increased endocannabinoid levels [50]. These increased levels would rather be expected to evoke an inhibition of memory acquisition. Therefore, the life-long elevated anandamide levels in this mutant mouse line possibly caused compensatory processes, leading finally to increased memory acquisition. Furthermore, CB1 receptor-deficient mice in the outbred strain CD1 [20] were reported to lack conditioned fear response in the fear conditioning test [51]. This latter observation is not in line with the results obtained with CB1 receptor-deficient mice in the inbred strain C57BL/6N [21] and needs further investigations. Reduced conditioned fear was reported in mice lacking TRPV1 ion channel [52], a receptor that is also activated by the endocannabinoid anandamide. Thus, it will be interesting to further understand the functional relation of the fear-promoting signaling via TRPV1 ion channel and the fear-alleviating signaling via CB1 receptors.

CB1 Receptors in Fear Extinction

The involvement of the ECS in the modulation of fear memories will be discussed below in detail, as there are several similarities linking the expression of fear and anxiety in humans that suffer from phobia, posttraumatic stress disorder (PTSD), and other anxiety disorders, to the expression of conditioned fear in animals [53, 54]. Understanding the mechanisms underlying fear extinction may lead to novel therapeutic concepts for the treatment of these disorders. In fact, the involvement of the ECS in these processes suggests that the ECS is a promising target system.

Fear Conditioning Paradigm

The paradigm of fear conditioning has been widely used to investigate the acquisition, consolidation, reconsolidation, and extinction of fear memory [55–59]. Different experimental designs are used. In background contextual fear conditioning, mice or rats receive a tone that is per se innocuous (e.g., 9 kHz at 80 dB for 20 s to 1 min). The tone co-terminates with a mild electric shock (about 0.5 to 1.0 mA for 1–2 s) delivered through the foot grid. This will induce an association of the tone with the shock, but also of the context (i.e., the conditioning chamber) with the shock. The strength and persistence of these associations can be evaluated in subsequent tests. In the version of the cued fear conditioning test, the tone alone is presented in a novel context (i.e., a cage of different shape, bedding, and other features). The first tone-alone exposure induces a conditioned response, which is quantified as the percentage of freezing behavior (i.e., no motion except of breathing) as normalized to the total duration of the tone presentation. As the animals expect a shock when the tone is presented, they freeze very strongly by only hearing the tone. The first non-reinforced exposure to the conditioned stimulus (i.e., to the tone) when performed after about 24 h will evaluate the acquisition and consolidation of fear memory. But at the same time, this non-reinforced presentation of the tone will initiate a process called extinction. The conditioned reaction (i.e., freezing) will start to gradually decrease. The freezing response can be further decreased by repetitive tone presentations. This is an adaptive reaction of the organism and is relevant for survival to adjust to new environmental situations [60–62]. In variation to this experimental design, it is also possible to present a light instead of a tone as a conditioned stimulus. In parallel, a contextual fear condi-

tioning test can be performed. Animals are placed into the conditioning chamber where they received the foot shock. Also in this experimental set-up, acquisition, consolidation, and extinction can be tested. In variance to the background contextual fear conditioning as described above, the foreground fear conditioning paradigm is also often performed. Here, during conditioning, a shock is paired only with the context without tone or light.

Different neuronal circuitries and brain regions are involved in these different tasks. Acquisition in cued fear conditioning involves in particular the amygdala, while acquisition in contextual fear conditioning involves both hippocampus and amygdala, although the brain regions and mechanisms involved in fear conditioning have become increasingly multifaceted [56]. The brain regions involved in extinction are still under investigations, but apart from amygdala and hippocampus, the prefrontal cortex is shown to be very important [63, 64].

During the recent years, research on extinction has gained a lot of attention, as it is believed that in humans, inappropriate extinction can contribute to disorders, such as PTSD [65]. It is an important and life-saving ability of the organism to adjust the behavior in an adequate manner after aversive memories have been acquired. If there are changes in the context, meaning, or relevance of previously acquired fear memory traces, the organism should guarantee flexibility in the behavioral reactions. Extinction is a behavioral mechanism, contributing to a decrease of fear response.

CB1 Receptor Signaling in the Extinction of Aversive Memories

The behavioral paradigm of fear conditioning with the possibility to investigate both acquisition and extinction processes has turned out to be very instrumental in obtaining novel insights into the physiological roles of the ECS in memory processing. Marsicano et al. [21] analyzed the behavioral changes in mice with a genetic deletion of the CB1 receptor. Unexpectedly, CB1 receptor-deficient mice showed normal acquisition and consolidation in the fear conditioning task, but fear extinction was strongly impaired. Impaired extinction was also observed when the CB1 receptor antagonist SR141716 was injected systemically into wild-type mice before the extinction trial, indicating that CB1 receptors are required at the moment of the extinction training, and supporting the notion that the phenotypic changes observed in CB1 receptor-deficient mice is not caused by developmental deficits, although the ECS has recently been shown to be involved in various processes in neural development [8, 66]. Further detailed analysis also showed that the ECS is important for both the extinction of fear within the extinction trial (i.e., short-term extinction) and in the decrease of freezing from one to the following extinction trial (i.e., long-term extinction). Furthermore, extinction was not completely abolished in $CB1^{-/-}$ mice, as increasing the numbers of extinction trials eventually led to extinction to a level of freezing comparable to the wild-type littermate controls. Several control experiments were able to exclude the possibility that the impairment of extinction might be caused by sensory-motor deficits or by increased anxiety under the experimental conditions used. In this study, the behavioral paradigm was designed in a manner to focus on amygdala-dependent learning (i.e., cued fear conditioning was applied). Thus, levels of endocannabinoids were determined in the amygdala immediately after the first tone presentation (i.e., after the extinction trial) in wild-type mice. It was found that both major endocannabinoids, anandamide, and 2-arachidonoyl glycerol, were strongly increased in the amygdala compared to control groups [21], indicating that the ECS is in fact activated in the amygdala at the moment of extinction and consistent with the observation that acute SR141716 treatment before the extinction trial strongly impairs short-term extinction. Later investigations showed that endocannabinoid levels were also increased in the hippocampus [67], consistent with the notion of an interplay between hippocampus and amygdala, as shown for oscillatory processes during fear memory retrieval [68]. Further studies have to address in detail the involvement of the ECS in the prefrontal cortex. In particular, the various subregions of the prefrontal cortex, such as the infralimbic and prelimbic cortex, must be considered as they play distinct roles in the process of extinction [69, 70]. Thus, these regions must be analyzed in follow-up studies, aiming at clarifying the previous observations [21].

As the study described above [21] has been published, the importance of CB1 receptors in the extinction of aversive memories has been substantiated by several groups in different behavioral paradigms [71–80]. In the investigation by Varvel and Lichtman [71], CB1 receptor-deficient mice were analyzed in the water maze task. Mice had to learn the location of an invisible escape platform in a small water tank. Both wild-type controls and CB1 receptor mutant mice were able to find the platform after several learning sessions with the same efficiency and accuracy. However, in the so-called reversal test, in which the position of the platform is placed into the opposite quadrant of the water pool, CB1 receptor-deficient mice showed a reduced capability to learn the change of position, and thus, they more frequently kept on swimming to the previous platform position. This reveals an impaired extinction of the previously acquired memory and an impaired flexibility to find the new position after the platform is changed. The water maze task intends to test spatial memory; however, as water is an uncommon, and thus, an aversive medium for mice, it can be assumed that it evokes a certain degree of stress. Thus, this assay monitors, in addition to the

extinction of spatial memory, also the extinction of aversive memory. Similar results were reported by Pamplona et al. [79], using the recently developed CB1 receptor antagonist SR147778 (1 mg/kg) [31] in the water maze task. After Wistar rats were trained to find the submerged platform, extinction trials were performed, in which the platform was placed into the opposite quadrant. SR147778 treatment before the extinction trial increased escape latency, i.e., decreased extinction. Another detailed study by Varvel et al. [72] employed the water maze task. Mice of the strain C57BL/6 acquired the memory to remember the quadrant where the submerged platform was present. In the extinction trials, no platform was present, thus, the previously learned behavior was not reinforced anymore. The authors used two different extinction protocols. In the "spaced" extinction protocol, when every 2–4 weeks, one extinction trial of 1 min was performed without the presence of the platform, $CB1^{-/-}$ mice and SR141716-treated mice, respectively, showed a clear impairment of extinction after five extinction trials compared to control groups. In contrast, in the "massed" extinction protocol, mice obtained four daily 2-min extinction trials over 5 days. Under this latter condition, all groups showed the same extinction, and no differences in the latency to get to the target quadrant were seen between CB1 receptor-deficient mice and control mice, and no effect of SR141716 was observed when applied before the extinction training. The reasons for these differences have not been understood yet. The lack of requirement of CB1 receptor signaling during "massed" extinction may point to the situation that under this intensive and also stressful situation, the CB1 receptor-mediated extinction process activated during the "spaced" extinction protocol has been overridden by other, unknown mechanisms. Clearly, it will be interesting to further understand the mechanisms underlying these differences of "spaced" vs "massed" extinction and the role of CB1 receptor function.

Suzuki et al. [74] investigated the role of CB1 receptors, using the contextual fear conditioning task in C57BL/6 mice. Systemic application of SR141716 (1 to 10 mg/kg) did not influence acquisition of fear memory. To differentiate whether CB1 receptors are involved in reconsolidation or extinction, mice were injected with SR141716, reexposed to the context for only 3 min, and freezing behavior was monitored 24 h later in the same context in a drug-free state. Blockade of CB1 receptor did not change freezing on the reexposure test (with the presence of SR141716) nor on the test day (drug-free). However, when the reexposure was performed for 30 min in the presence of SR141716, freezing during reexposure was not influenced, but on the test day, 24 h later, freezing response was enhanced compared to vehicle controls. Thus, CB1 receptors are involved in the extinction of contextual fear memory, but not in reconsolidation processes. Secondly, in this behavioral test, CB1 receptors did not influence within-session extinction (i.e., short-term extinction), but had only affected long-term extinction. This finding is consistent with the observations by Pamplona et al. [79], who showed that freezing was not significantly influenced by the CB1 receptor antagonist SR141716 during the first 9-min context exposure after contextual fear conditioning, while SR141716 impaired fear extinction during the second and third context exposure. This apparent role of CB1 receptors in long-term extinction, but not in short-term extinction in contextual fear conditioning task, is in contrast with the cued fear conditioning task [21] and with the fear potentiated startle [73, 77]. In these behavioral tests, both short- and long-term extinction was reported to require CB1 receptor function.

To broaden the concept that CB1 receptors are involved in extinction of aversive memories, the passive avoidance task was employed in C57BL/6J mice [80]. In an apparatus with a free choice to enter the lit or the dark compartment, mice received a shock in the dark compartment in the one-trial training session. For the extinction learning, mice were placed into the lit compartment and were then allowed to enter the dark compartment, where they did not receive a shock. After several sessions, the mice learned that the dark compartment was not paired with a shock, and the latency to enter this compartment decreased. Treatment with SR141716 before the extinction training increases the latency to enter the dark compartment, thus, extinction was impaired.

An interesting behavioral paradigm was used by Shiflett et al. [81]. Food-storing birds demonstrate remarkable memory ability in recalling the locations of thousands of hidden food caches. Intra-hippocampal infusions of the CB1 receptor antagonist SR141716 enhanced long-term memory for the location of a hidden food reward, as measured 72 h after acquisition. However, when the location of the food reward was changed after the acquisition phase, birds that had received SR141716 during initial learning showed impairments in recalling the most recent reward location. Thus, blocking of CB1 receptor function appears to lead to more robust, long-lasting memories, but these memories reduced the flexibility and adaptation of the organisms to change according to new environmental conditions. This result resembles those obtained from the water maze task in mice, where blockade of CB1 receptors affect the behavior in the reversal task.

Extinction in Appetitive Operant Learning Tasks

In the further explorations, it was asked whether or not CB1 receptors are only involved in the extinction of aversive memory, or whether there is also a role in the extinction of non-aversive memories. For this, a food-motivated task was used [82]. Mice had to learn to poke into a hole at the position of a flashing light to obtain a food reward. After

numerous sessions, mice were able to learn this task. To investigate the involvement of CB1 receptor in this task, $CB1^{-/-}$ mice and wild-type littermates were used. Due to the fact that CB1 receptors are known to be involved in the incentive behavior to search for food [83–85], $CB1^{-/-}$ mice had to be starved slightly more than the wild-type littermates to obtain mice with a similar motivation to search for food. Finally, both groups were able to poke into the correct hole with a high accuracy. A retention test 1 week later showed similar performance in both groups; thus, CB1 receptors are not involved in the consolidation of this memory. The extinction test was performed similarly as the acquisition phase. It was performed under slight food restriction, and no food reward was given when the correct hole was poked. This led to extinction of the behavior due to the lack of reinforcement. Remarkably, no differences were observed between the two genotypes. Thus, CB1 receptors are not required in this appetitively motivated behavior. Recently, this finding was supported by the study of Niyuhire et al. [80]. C57BL/6J mice had to learn to press a lever to obtain a sweetened milk reward. Mice were drug-free during the acquisition of the task. Then, SR141716 was injected before each extinction training, in which the pressing of the lever did not lead to the milk reward. Thus, the frequency of lever pressing gradually decreased. Blockade of CB1 receptors did not change the rate of extinction, being consistent with the results by Hölter et al. [82].

Intracellular Signaling During Extinction

In a first attempt to understand intracellular signaling systems that are dysregulated in CB1 receptor-deficient mice and that might be involved in the extinction learning, candidate protein kinases and phosphatases were investigated by analyzing distinct brain areas immediately after extinction training by using Western blotting [76]. The cued fear conditioning paradigm was used as described [21]. When samples were analyzed 30 min after extinction training (i.e., tone presentation) and levels were compared with no-tone control subjects, CB1 receptor-deficient mice failed to show an increase of mitogen-activated protein (MAP) kinase phosphorylation and of calcineurin protein in the basolateral amygdala. Such an increase is, however, observed in wild-type littermates. This is consistent with previous findings that these biochemical changes are required for fear extinction [86, 87], and they are defective in CB1 receptor-deficient mice, which are also impaired in extinction.

Sensitization and Habituation-Like Processes

In the study by Kamprath et al. [67], the question was posed as to whether or not the ECS is involved in non-associative extinction processes, as it was previously shown that freezing responses of conditioned mice to the tone are determined by both associative and non-associative memory components [88]. To this end, a sensitization paradigm was used. Sensitization is a non-associative learning process, which is characterized by enhanced responsiveness to potentially harmful stimuli, after the organism had encountered a traumatic, stressful, or aversive event. Sensitization was evoked by applying an inescapable foot shock to mice. In the subsequent test sessions, mice were exposed to a tone in a novel context. Although the tone was innocuous before sensitization has occurred, the sensitized mice show strong freezing. By using this paradigm, the role of CB1 receptors was investigated in detail, finally leading to the conclusions that CB1 receptors are involved primarily in a habituation-like process and that they are dispensable for associative safety learning. In safety learning, animals form an association between the tone and the non-appearance of the predicted punishment (i.e., foot shock), finally leading to a suppression of the tone-shock association. This process is called extinction, as discussed already above [60, 61]. In habituation-like processes, in contrast, repeated non-reinforced tone presentations lead to a decrease in responsiveness to the tone [89]. Regardless of the mechanistic and theoretical interpretations [61] of the results obtained by Kamprath et al. [67], the findings are very relevant per se. The role of the ECS in the control of long-term extinction may have some relation to the regulation of the stress axis, as several studies identified a function of the ECS in the adaptation to stress responses [90, 91], although some divergent results exist [92]. Nevertheless, CB1 receptor deficiency can lead to a hyperactivity of the hypothalamic-pituitary-adrenal axis [90, 93, 94], and the ECS can mediate the habituation after repeated restraint stress [95]. Altogether, these results indicate that extinction of aversive memories via a habituation-like process and the adaptation to stress responses via the alleviation of the stress axis are, in part, controlled by the ECS.

CB1 Receptors and the Enhancement of Fear Adaptation

Starting from the clear and consistent results using CB1 receptor-deficient mice and CB1 receptor antagonists in blocking fear extinction, it has become an interesting and clinically relevant issue to ask whether or not a stimulation of CB1 receptor signaling in addition to the endogenous signaling process during extinction training might be beneficial and might be able to accelerate the extinction rate. The results obtained so far from experiments in rodents allow suggesting that in principle, it is possible to

accelerate fear adaptation by additional CB1 receptor stimulation. This is very promising for potential therapeutic applications in humans. However, in contrast to the experiments in which CB1 receptor function was blocked by genetic or pharmacological tools, the alleviating effects after CB1 receptor stimulation have not been observed consistently. Thus, further detailed studies are required to understand under which circumstances exactly the beneficial effects are achievable.

Pharmacological Studies

Chhatwal et al. [73] were the first to be able to substantiate the concept of enhanced extinction. They investigated fear-potentiated startle in male Sprague-Dawley rats. Systemic application of AM404 (10 mg/kg), an inhibitor of endocannabinoid membrane transport [33], before extinction training facilitated the retention of extinction memory. Treated rats showed decreased fear 1 and 24 h after extinction training compared to controls. In addition, AM404-treated animals displayed decreased shock-induced reinstatement of fear. This latter observation is relevant as it fuels the hope that extinction memory after AM404 application is more robust and less susceptible to resumed stress and fear context than extinction without pharmacological treatment. The effect of AM404 was abolished when the CB1 receptor antagonist SR141716 was co-applied, indicating a CB1 receptor-dependent process. Control experiments ruled out influences of AM404 on analgesia, locomotion and expression of conditioned fear. The authors also studied the effects of WIN 55-212,2 (5 mg/kg), a potent CB1 receptor agonist. At this high dose, extinction was not enhanced, but rather, the levels of conditioned fear 24 h after extinction training were slightly, but nonsignificantly higher than in the vehicle controls.

Congruent results were found using an inhibitor of the anandamide degrading enzyme fatty acid amide hydrolase (FAAH), OL-135 [50]. In this study, male C57BL/6 mice were trained in eight sessions in the water maze task using a fixed hidden platform. After memory acquisition, four probe trials without platform were performed in the water tank. Extinction was monitored as a decrease of time spent in the quadrant where the platform was previously present during the acquisition phase. Indeed, the treatment with the FAAH inhibitor OL-135 (30 mg/kg) 30 min before the extinction trials was able to decrease the time spent in the former target quadrant compared to vehicle controls, thus, showing that OL-135 is able to enhance the rate of extinction. The effect was clearly CB1 receptor-mediated, as the CB1 antagonist SR141716 blocked the effect of OL-135. THC in various doses (from 0.1 to 10 mg/kg) failed to accelerate extinction.

A recent study by Pamplona et al. [79] was able to show that WIN 55-212,2 at a low dose of 0.25 mg/kg, but not at 2.5 mg/kg, facilitated the extinction of contextual fear in the fear conditioning task and spatial memory in the water maze reversal task, using male Wistar rats. Extinction of both recent (1-day old) and remote (30-day old) contextual fear memory were facilitated by the CB1 receptor agonist, an effect that was abolished by coadministration of the CB1 receptor antagonist SR141716. Several control experiments underlined the specificity of the facilitated extinction by WIN 55-212,2. The retrieval of contextual fear memory, i.e., the freezing response to the context 1 day after fear conditioning, was unaffected by the prior administration of the CB1 receptor agonist. Furthermore, no apparent effects on within-session extinction were observed. Unconditioned freezing and locomotion were not changed by the beneficial dose of 0.25 mg/kg WIN 55-212,2. This was the first report showing enhanced extinction induced by a systemic application of a CB1 receptor agonist before the extinction trial. A treatment with THC, however, was not reported in this study. THC would be therapeutically very interesting, as it contains the approval for the use in humans. However, WIN 55-212,2 and THC have a rather different pharmacological profile on cannabinoid receptors [3], and thus, it will be interesting whether or not similar experiments as published by Pamplona et al. can be repeated using THC. In addition, such experiments should be repeated in mice.

A study by Lin et al. [78] addressed the effects of CB1 receptor activation on reconsolidation of fear memory. Adult rats were used in the fear-potentiated startle test. Rats were trained in the startle box and received ten light-foot shock pairings. Twenty-four hours later, fear-potentiated startle was tested in one short session (test 1). Within 1 h after this test, the CB1 receptor agonists HU210 or WIN 55-212,2 alone or in combination with the CB1 receptor antagonist AM251 were injected bilaterally into the amygdala. Rats were re-tested 1 day later (test 2), addressing the question whether or not reconsolidation was affected. In fact, injection of CB1 receptor agonists led to an impairment of reconsolidation of the reactivated memory in test 1, as measured by decreased freezing behavior in test 2. In addition, CB1 receptor activation in the amygdala also suppressed reinstatement and spontaneous recovery, two relevant features from the point of view for the potential therapeutic applications of CB1 receptor agonists. These effects were completely blocked by co-application of CB1 receptor agonists with AM251. Furthermore, application of the CB1 receptor blocker AM251 alone had no effect on reconsolidation, suggesting an involvement of exogenous, but not of endogenous cannabinoids in the process of reconsolidation.

Altogether, these results by Lin et al. [78] are very similar to a study using protein synthesis blocker immediately after memory reactivation [96], and it appears that the CB1 receptor agonists induce amnesia during the reactiva-

tion of the memory (test 1). This is in contrast to the view outlined above, arguing that CB1 receptors are involved in the control of the extinction of aversive memories. Further studies are required to address this issue. It might be the case that depending on the experimental conditions, activation of CB1 receptor by an exogenous agonist may facilitate extinction or block reconsolidation.

Using the conditioned taste aversion (CTA) paradigm, a recent study found [97] that CB1 receptor activation by injection of WIN 55,212-2 into the insular cortex inhibited reconsolidation, but not extinction, while injection of the CB1 receptor antagonist SR141716 blocked extinction of CTA, but not reconsolidation. The underlying mechanisms have still to be elucidated, but clearly, the behavioral paradigm of CTA offers the opportunity to detail the differential roles of the ECS, CB1 receptors and exogenous cannabinoids in reconsolidation and extinction processes.

Oleamide, another bioactive lipid with similarities to endocannabinoids, was shown to facilitate extinction of aversive memory in male Wistar rats [98]. Rats were trained in the passive avoidance test using a foot shock as described above. They were injected immediately after training systemically with oleamide (30 or 50 mg/kg). Twenty-four hours later, inhibitory avoidance was tested. It was found that in the first exposure, oleamide and vehicle treated animals showed no differences in latency to enter the compartment where the foot shock was delivered. Further exposures without drug treatments revealed that oleamide-treated rats extinguished the aversive memory faster. Oleamide also reduced core body temperature and showed analgesic effects in the tail flick test. The underlying mechanisms are not clear, and further experiments are clearly needed to answer several questions: Is the effect oleamide CB1 receptor-mediated? What is the effect of oleamide when injected before and after the extinction trials, respectively?

An interesting study was reported by Parker et al. [99] on the extinction of cocaine- and amphetamine-induced conditioned place preference (CPP). In several sessions, injection of cocaine and amphetamine, respectively, were paired with one of the two distinctive floors of the CPP apparatus. Place preference to the treatment-paired floor compared to the non-treatment-paired floor has established. In the extinction training without cocaine or amphetamine, rats received either THC (0.5 mg/kg) or cannabidiol (5 mg/kg) before the exposure to the CPP apparatus. Two days later, animals were tested for the preference to the treatment-paired floor. Rats treated with THC or cannabidiol showed decreased preference for the treatment-paired floor compared to the vehicle-treated group. It is important to note that the CB1 receptor antagonist SR141716 was not able to abolish the effects of THC and cannabidiol, suggesting a non-CB1 receptor-mediated signaling. Thus, further studies will be needed to understand the underlying mechanisms.

Genetic Studies

To date, the only way to genetically enhance the endocannabinoid signaling was achieved by the generation of mice deficient for FAAH, leading to 10 to 15 times increased basal levels of anandamide [27]. These mice provide a valuable tool for behavioral analyses. Consistent with the results obtained by using the FAAH inhibitor OL-135 in the water maze task, FAAH-deficient mice displayed an enhanced extinction rate compared to wild-type control mice in a C57BL/6 background [50].

Endocannabinoids, Synaptic Plasticity, and Extinction

Endocannabinoids and CB1 receptors have been shown to mediate short-term and long-term modulatory processes in synaptic transmission [24, 25]. In general, the activation of the endocannabinoid system at the synapse leads to a short or a sustained suppression of neurotransmitter release from the presynapse. This modulation can occur at both excitatory and inhibitory synapses in numerous brain regions, including those that are centrally involved in extinction of fear memories, i.e., in amygdala [21, 100, 101], hippocampus [101–104], and prefrontal areas [105]. However, the process of extinction involves a complex neuronal circuitry [106], and it remains to be determined which sites of CB1 receptor expression are centrally involved in the CB1 receptor-mediated extinction of fear memories. Further studies using conditional CB1 receptor knock-out mice [23] should help in elucidating these questions.

Conclusion and Perspectives

The fear alleviating effects after application of drugs that are able to enhance the signaling via CB1 receptors have been shown in a few cases, but further detailed studies are required, as the effects observed are not robust. Several studies reported that CB1 receptor activation did not lead to any effects or even to non-beneficial effects. This may be caused by the fact that many parameters have to be considered in these experiments, including differences in the behavioral paradigms, route of drug application, dose of drug, and species and strain differences in the behavioral paradigms. In addition, the complexity of the mechanism underlying the alleviation of fear memory may exceed those involved in the acquisition of fear memories. The mechanisms underlying the ECS-mediated extinction of

aversive memories are not fully understood yet. Using conditional mutagenesis [22, 23], the brain regions and neuronal subpopulation involved in this process have to be identified. The interrelation between the control of extinction and the regulation of the stress axis by the ECS should be analyzed in detail [90, 91]. Finally, more accurate animal models for human anxiety disorders, such as PTSD, must be applied for these analyses [107].

Currently, there are no published data available from studies in humans whether or not the therapeutic concept of an increased activity of CB1 receptors could be beneficial for humans suffering from generalized anxiety disorders, phobia, or PTSD.

Acknowledgements I would like to thank Drs. Krisztina Monory and Fabricio Moreira for critically reading the manuscript and the generous support by the Hübner Stiftung.

References

1. Piomelli D (2003) The molecular logic of endocannabinoid signalling. Nat Rev Neurosci 4:873–884
2. Di Marzo V, De Petrocellis L, Bisogno T (2005) The biosynthesis, fate and pharmacological properties of endocannabinoids. Handb Exp Pharmacol 168:147–185
3. Pertwee RG (2005) Pharmacological actions of cannabinoids. Handb Exp Pharmacol 168:1–51
4. Valverde O, Karsak M, Zimmer A (2005) Analysis of the endocannabinoid system by using CB1 cannabinoid receptor knockout mice. Handb Exp Pharmacol 168:117–145
5. Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R (2006) The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocr Rev 27:73–100
6. Mackie K (2006) Cannabinoid receptors as therapeutic targets. Annu Rev Pharmacol Toxicol 46:101–122
7. Matias I, Di Marzo V (2007) Endocannabinoids and the control of energy balance. Trends Endocrinol Metab 18:27–37
8. Harkany T, Guzman M, Galve-Roperh I, Berghuis P, Devi LA, Mackie K (2007) The emerging functions of endocannabinoid signaling during CNS development. Trends Pharmacol Sci 28:83–92
9. Wotjak CT (2005) Role of endogenous cannabinoids in cognition and emotionality. Mini Rev Med Chem 5:659–670
10. Sullivan JM (2000) Cellular and molecular mechanisms underlying learning and memory impairments produced by cannabinoids. Learn Mem 7:132–139
11. Riedel G, Davies SN (2005) Cannabinoid function in learning, memory and plasticity. Handb Exp Pharmacol 168:445–477
12. Ranganathan M, D'Souza DC (2006) The acute effects of cannabinoids on memory in humans: a review. Psychopharmacology (Berl) 188:425–444
13. Lichtman AH, Varvel SA, Martin BR (2002) Endocannabinoids in cognition and dependence. Prostaglandins Leukot. Essent Fatty Acids 66:269–285
14. Robbe D, Montgomery SM, Thome A, Rueda-Orozco PE, McNaughton BL, Buzsaki G (2006) Cannabinoids reveal importance of spike timing coordination in hippocampal function. Nat Neurosci 9:1526–1533
15. Freund TF, Katona I, Piomelli D (2003) Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 83:1017–1066
16. Mackie K (2005) Distribution of cannabinoid receptors in the central and peripheral nervous system. Handb Exp Pharmacol 168:299–325
17. Marsicano G, Lutz B (1999) Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. Eur J Neurosci 11:4213–4225
18. Lutz B (2002) Molecular biology of cannabinoid receptors. Prostaglandins Leukot Essent Fatty Acids 66:123–142
19. Zimmer A, Zimmer AM, Hohmann AG, Herkenham M, Bonner TI (1999) Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. Proc Natl Acad Sci USA 96:5780–5785
20. Ledent C, Valverde O, Cossu G, Petitet F, Aubert JF, Beslot F, Bohme GA, Imperato A, Pedrazzini T, Roques BP, Vassart G, Fratta W, Parmentier M (1999) Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. Science 283:401–404
21. Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG, Hermann H, Tang J, Hofmann C, Zieglgansberger W, Di Marzo V, Lutz B (2002) The endogenous cannabinoid system controls extinction of aversive memories. Nature 418:530–534
22. Marsicano G, Goodenough S, Monory K, Hermann H, Eder M, Cannich A, Azad SC, Cascio MG, Gutierrez SO, van der Stelt M, Lopez-Rodriguez ML, Casanova E, Schütz G, Zieglgänsberger W, Di Marzo V, Behl C, Lutz B (2003) CB1 cannabinoid receptors and on-demand defense against excitotoxicity. Science 302:84–88
23. Monory K, Massa F, Egertova M, Eder M, Blaudzun H, Westenbroek R, Kelsch W, Jacob W, Marsch R, Ekker M, Long J, Rubenstein JL, Goebbels S, Nave KA, During M, Klugmann M, Wolfel B, Dodt HU, Zieglgänsberger W, Wotjak CT, Mackie K, Elphick MR, Marsicano G, Lutz B (2006) The endocannabinoid system controls key epileptogenic circuits in the hippocampus. Neuron 51:455–466
24. Chevaleyre V, Takahashi KA, Castillo PE (2006) Endocannabinoid-mediated synaptic plasticity in the CNS. Annu Rev Neurosci 29:37–76
25. Marsicano G, Lutz B (2006) Neuromodulatory functions of the endocannabinoid system. J Endocrinol Invest 29:27–46
26. Klein TW (2005) Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol 5:400–411
27. Cravatt BF, Demarest K, Patricelli MP, Bracey MH, Giang DK, Martin BR, Lichtman AH (2001) Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. Proc Natl Acad Sci USA 98:9371–9376
28. Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, Koltzenburg M, Basbaum AI, Julius D (2000) Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 288:306–313
29. Rinaldi-Carmona M, Barth F, Heaulme M, Shire D, Calandra B, Congy C, Martinez S, Maruani J, Neliat G, Caput D, Ferrara P, Soubrié P, Brelière JC, Le Fur G (1994) SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 350:240–244
30. Gatley SJ, Gifford AN, Volkow ND, Lan R, Makriyannis A (1996) 123I-labeled AM251: a radioiodinated ligand which binds in vivo to mouse brain cannabinoid CB1 receptors. Eur J Pharmacol 307:331–338
31. Rinaldi-Carmona M, Barth F, Congy C, Martinez S, Oustric D, Perio A, Poncelet M, Maruani J, Arnone M, Finance O, Soubrie P, Le Fur G (2004) SR147778 [5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethyl-*N*-(1-piperidinyl)-1H-pyr azole-3-carboxamide], a new potent and selective antagonist of the CB1

cannabinoid receptor: biochemical and pharmacological characterization. J Pharmacol Exp Ther 310:905–914
32. Kathuria S, Gaetani S, Fegley D, Valino F, Duranti A, Tontini A, Mor M, Tarzia G, Rana GL, Calignano A, Giustino A, Tattoli M, Palmery M, Cuomo V, Piomelli D (2003) Modulation of anxiety through blockade of anandamide hydrolysis. Nat Med 9:76–81
33. Beltramo M, Stella N, Calignano A, Lin SY, Makriyannis A, Piomelli D (1997) Functional role of high-affinity anandamide transport, as revealed by selective inhibition. Science 277:1094–1097
34. De Petrocellis L, Bisogno T, Davis JB, Pertwee RG, Di Marzo V (2000) Overlap between the ligand recognition properties of the anandamide transporter and the VR1 vanilloid receptor: inhibitors of anandamide uptake with negligible capsaicin-like activity. FEBS Lett 483:52–56
35. Lopez-Rodriguez ML, Viso A, Ortega-Gutierrez S, Lastres-Becker I, Gonzalez S, Fernandez-Ruiz J, Ramos JA (2001) Design, synthesis and biological evaluation of novel arachidonic acid derivatives as highly potent and selective endocannabinoid transporter inhibitors. J Med Chem 44:4505–4508
36. de Sousa N, Almeida OF, Wotjak CT (2006) A hitchhiker's guide to behavioral analysis in laboratory rodents. Genes Brain Behav 5(Suppl 2):5–24
37. Reibaud M, Obinu MC, Ledent C, Parmentier M, Bohme GA, Imperato A (1999) Enhancement of memory in cannabinoid CB1 receptor knock-out mice. Eur J Pharmacol 379:R1–R2
38. Maccarrone M, Valverde O, Barbaccia ML, Castane A, Maldonado R, Ledent C, Parmentier M, Finazzi-Agro A (2002) Age-related changes of anandamide metabolism in CB1 cannabinoid receptor knockout mice: correlation with behaviour. Eur J Neurosci 15:1178–1186
39. Martin M, Ledent C, Parmentier M, Maldonado R, Valverde O (2002) Involvement of CB1 cannabinoid receptors in emotional behaviour. Psychopharmacology (Berl) 159:379–387
40. Bilkei-Gorzo A, Racz I, Valverde O, Otto M, Michel K, Sastre M, Zimmer A (2005) Early age-related cognitive impairment in mice lacking cannabinoid CB1 receptors. Proc Natl Acad Sci USA 102:15670–15675
41. Lutz B (2004) On-demand activation of the endocannabinoid system in the control of neuronal excitability and epileptiform seizures. Biochem Pharmacol 68:1691–1698
42. van der Stelt M, Di Marzo V (2005) Cannabinoid receptors and their role in neuroprotection. Neuromolecular Med 7:37–50
43. Terranova JP, Storme JJ, Lafon N, Perio A, Rinaldi-Carmona M, LeFur G, Soubrie P (1996) Improvement of memory in rodents by the selective CB1 cannabinoid receptor antagonist, SR141716. Psychopharmacology 126:165–172
44. Lichtman AH (2000) SR 141716A enhances spatial memory as assessed in a radial-arm maze task in rats. Eur J Pharmacol 404:175–179
45. Wolff MC, Leander JD (2003) SR141716A, a cannabinoid CB1 receptor antagonist, improves memory in a delayed radial maze task. Eur J Pharmacol 477:213–217
46. Mallet PE, Beninger RJ (1998) The cannabinoid CB1 receptor antagonist SR141716A attenuates the memory impairment produced by delta9-tetrahydrocannabinol or anandamide. Psychopharmacology (Berl) 140:11–19
47. Hampson RE, Deadwyler SA (2000) Cannabinoids reveal the necessity of hippocampal neural encoding for short-term memory in rats. J Neurosci 20:8932–8942
48. Mansbach RS, Rovetti CC, Winston EN, Lowe JA III (1996) Effects of the cannabinoid CB1 receptor antagonist SR141716A on the behavior of pigeons and rats. Psychopharmacology (Berl) 124:315–322
49. Kishimoto Y, Kano M (2006) Endogenous cannabinoid signaling through the CB1 receptor is essential for cerebellum-dependent discrete motor learning. J Neurosci 26:8829–8837
50. Varvel SA, Wise LE, Niyuhire F, Cravatt BF, Lichtman AH (2007) Inhibition of fatty-acid amide hydrolase accelerates acquisition and extinction rates in a spatial memory task. Neuropsychopharmacology 32:1032–1041
51. Mikics E, Dombi T, Barsvari B, Varga B, Ledent C, Freund TF, Haller J (2006) The effects of cannabinoids on contextual conditioned fear in CB1 knockout and CD1 mice. Behav Pharmacol 17:223–230
52. Marsch R, Foeller E, Rammes G, Bunck M, Kossl M, Holsboer F, Zieglgänsberger W, Landgraf R, Lutz B, Wotjak CT (2007) Reduced anxiety, conditioned fear, and hippocampal long-term potentiation in transient receptor potential vanilloid type 1 receptor-deficient mice. J Neurosci 27:832–839
53. Brewin CR (2001) A cognitive neuroscience account of posttraumatic stress disorder and its treatment. Behav Res Ther 39:373–393
54. Nemeroff CB, Bremner JD, Foa EB, Mayberg HS, North CS, Stein MB (2006) Posttraumatic stress disorder: a state-of-the-science review. J Psychiatr Res 40:1–21
55. LeDoux JE (2000) Emotion circuits in the brain. Annu Rev Neurosci 23:155–184
56. Kim JJ, Jung MW (2006) Neural circuits and mechanisms involved in Pavlovian fear conditioning: a critical review. Neurosci Biobehav Rev 30:188–202
57. Rodrigues SM, Schafe GE, LeDoux JE (2004) Molecular mechanisms underlying emotional learning and memory in the lateral amygdala. Neuron 44:75–91
58. Maren S, Quirk GJ (2004) Neuronal signalling of fear memory. Nat Rev Neurosci 5:844–852
59. Wotjak CT (2005) Learning and memory. Handb Exp Pharmacol 169:1–34
60. Myers KM, Davis M (2002) Behavioral and neural analysis of extinction. Neuron 36:567–584
61. Myers KM, Davis M (2007) Mechanisms of fear extinction. Mol Psychiatry 12:120–150
62. Barad M, Gean PW, Lutz B (2006) The role of the amygdala in the extinction of conditioned fear. Biol Psychiatry 60:322–328
63. Quirk GJ, Garcia R, Gonzalez-Lima F (2006) Prefrontal mechanisms in extinction of conditioned fear. Biol Psychiatry 60:337–343
64. Sotres-Bayon F, Cain CK, LeDoux JE (2006) Brain mechanisms of fear extinction: historical perspectives on the contribution of prefrontal cortex. Biol Psychiatry 60:329–336
65. Milad MR, Rauch SL, Pitman RK, Quirk GJ (2006) Fear extinction in rats: implications for human brain imaging and anxiety disorders. Biol Psychol 73:61–71
66. Berghuis P, Rajnicek AM, Morozov YM, Ross RA, Mulder J, Urban GM, Monory K, Marsicano G, Matteoli M, Canty A, Irving AJ, Katona I, Yanagawa Y, Rakic P, Lutz B, Mackie K, Harkany T (2007) Hardwiring the brain: endocannabinoids shape neuronal connectivity. Science 316:1212–1216
67. Kamprath K, Marsicano G, Tang J, Monory K, Bisogno T, Di Marzo V, Lutz B, Wotjak CT (2006) Cannabinoid CB1 receptor mediates fear extinction via habituation-like processes. J Neurosci 26:6677–6686
68. Seidenbecher T, Laxmi TR, Stork O, Pape HC (2003) Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. Science 301:846–850
69. Burgos-Robles A, Vidal-Gonzalez I, Santini E, Quirk GJ (2007) Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex. Neuron 53:871–880

70. Vidal-Gonzalez I, Vidal-Gonzalez B, Rauch SL, Quirk GJ (2006) Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear. Learn Mem 13:728–733
71. Varvel SA, Lichtman AH (2002) Evaluation of CB1 receptor knockout mice in the Morris water maze. J Pharmacol Exp Ther 301:915–924
72. Varvel SA, Anum EA, Lichtman AH (2005) Disruption of CB1 receptor signaling impairs extinction of spatial memory in mice. Psychopharmacology (Berl) 179:863–872
73. Chhatwal JP, Davis M, Maguschak KA, Ressler KJ (2005) Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear. Neuropsychopharmacology 30:516–524
74. Suzuki A, Josselyn SA, Frankland PW, Masushige S, Silva AJ, Kida S (2004) Memory reconsolidation and extinction have distinct temporal and biochemical signatures. J Neurosci 24:4787–4795
75. Finn DP, Beckett SR, Richardson D, Kendall DA, Marsden CA, Chapman V (2004) Evidence for differential modulation of conditioned aversion and fear-conditioned analgesia by CB1 receptors. Eur J Neurosci 20:848–852
76. Cannich A, Wotjak CT, Kamprath K, Hermann H, Lutz B, Marsicano G (2004) CB1 cannabinoid receptors modulate kinase and phosphatase activity during extinction of conditioned fear in mice. Learn Mem 11:625–632
77. Chhatwal JP, Stanek-Rattiner L, Davis M, Ressler KJ (2006) Amygdala BDNF signaling is required for consolidation but not encoding of extinction. Nat Neurosci 9:870–872
78. Lin HC, Mao SC, Gean PW (2006) Effects of intra-amygdala infusion of CB1 receptor agonists on the reconsolidation of fear-potentiated startle. Learn Mem 13:316–321
79. Pamplona FA, Prediger RD, Pandolfo P, Takahashi RN (2006) The cannabinoid receptor agonist WIN 55,212-2 facilitates the extinction of contextual fear memory and spatial memory in rats. Psychopharmacology (Berl) 188:641–649
80. Niyuhire F, Varvel SA, Thorpe AJ, Stokes RJ, Wiley JL, Lichtman AH (2007) The disruptive effects of the CB(1) receptor antagonist rimonabant on extinction learning in mice are task-specific. Psychopharmacology (Berl) 191:223–231
81. Shiflett MW, Rankin AZ, Tomaszycki ML, DeVoogd TJ (2004) Cannabinoid inhibition improves memory in food-storing birds, but with a cost. Proc R Soc Lond B Biol Sci 271:2043–2048
82. Hölter SM, Kallnik M, Wurst W, Marsicano G, Lutz B, Wotjak CT (2005) Cannabinoid CB1 receptor is dispensable for memory extinction in an appetitively-motivated learning task. Eur J Pharmacol 510:69–74
83. Sanchis-Segura C, Cline BH, Marsicano G, Lutz B, Spanagel R (2004) Reduced sensitivity to reward in CB1 knockout mice. Psychopharmacology (Berl) 176:223–232
84. Thornton-Jones ZD, Kennett GA, Vickers SP, Clifton PG (2007) A comparison of the effects of the CB(1) receptor antagonist SR141716A, pre-feeding and changed palatability on the microstructure of ingestive behaviour. Psychopharmacology (Berl) 193:1–9
85. Thornton-Jones ZD, Vickers SP, Clifton PG (2005) The cannabinoid CB1 receptor antagonist SR141716A reduces appetitive and consummatory responses for food. Psychopharmacology (Berl) 179:452–460
86. Lin CH, Yeh SH, Leu TH, Chang WC, Wang ST, Gean PW (2003) Identification of calcineurin as a key signal in the extinction of fear memory. J Neurosci 23:1574–1579
87. Lu KT, Walker DL, Davis M (2001) Mitogen-activated protein kinase cascade in the basolateral nucleus of amygdala is involved in extinction of fear-potentiated startle. J Neurosci 21:RC162
88. Kamprath K, Wotjak CT (2004) Nonassociative learning processes determine expression and extinction of conditioned fear in mice. Learn Mem 11:770–786
89. McSweeney FK, Swindell S (2002) Common processes may contribute to extinction and habituation. J Gen Psychol 129:364–400
90. Viveros MP, Marco EM, File SE (2005) Endocannabinoid system and stress and anxiety responses. Pharmacol Biochem Behav 81:331–342
91. Hill MN, Gorzalka BB (2005) Is there a role for the endocannabinoid system in the etiology and treatment of melancholic depression? Behav Pharmacol 16:333–352
92. Witkin JM, Tzavara ET, Davis RJ, Li X, Nomikos GG (2005) A therapeutic role for cannabinoid CB1 receptor antagonists in major depressive disorders. Trends Pharmacol Sci 26:609–617
93. Cota D, Marsicano G, Tschöp M, Grübler Y, Flachskamm C, Schubert M, Auer D, Yassouridis A, Thone-Reineke C, Ortmann S, Tomassoni F, Cervino C, Nisoli E, Linthorst AC, Pasquali R, Lutz B, Stalla GK, Pagotto U (2003) The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. J Clin Invest 112:423–431
94. Cota D, Steiner MA, Marsicano G, Cervino C, Herman JP, Grubler Y, Stalla J, Pasquali R, Lutz B, Stalla GK, Pagotto U (2007) Requirement of cannabinoid receptor type 1 for the basal modulation of hypothalamic-pituitary-adrenal axis function. Endocrinology 148:1574–1581
95. Patel S, Roelke CT, Rademacher DJ, Hillard CJ (2005) Inhibition of restraint stress-induced neural and behavioural activation by endogenous cannabinoid signalling. Eur J Neurosci 21:1057–1069
96. Nader K, Schafe GE, Le Doux JE (2000) Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406:722–726
97. Kobilo T, Hazvi S, Dudai Y (2007) Role of cortical cannabinoid CB1 receptor in conditioned taste aversion memory. Eur J Neurosci 25:3417–3421
98. Murillo-Rodriguez E, Giordano M, Cabeza R, Henriksen SJ, Mendez DM, Navarro L, Prospero-Garcia O (2001) Oleamide modulates memory in rats. Neurosci Lett 313:61–64
99. Parker LA, Burton P, Sorge RE, Yakiwchuk C, Mechoulam R (2004) Effect of low doses of delta9-tetrahydrocannabinol and cannabidiol on the extinction of cocaine-induced and amphetamine-induced conditioned place preference learning in rats. Psychopharmacology (Berl) 175:360–366
100. Azad SC, Monory K, Marsicano G, Cravatt BF, Lutz B, Zieglgansberger W, Rammes G (2004) Circuitry for associative plasticity in the amygdala involves endocannabinoid signaling. J Neurosci 24:9953–9961
101. Chevaleyre V, Heifets BD, Kaeser PS, Sudhof TC, Purpura DP, Castillo PE (2007) Endocannabinoid-mediated long-term plasticity requires cAMP/PKA signaling and RIM1alpha. Neuron 54:801–812
102. Chevaleyre V, Castillo PE (2004) Endocannabinoid-mediated metaplasticity in the hippocampus. Neuron 43:871–881
103. Wilson RI, Nicoll RA (2001) Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature 410:588–592
104. Alger E (2002) Retrograde signaling in the regulation of synaptic transmission: focus on endocannabinoids. Prog Neurobiol 68:247–286
105. Lafourcade M, Elezgarai I, Mato S, Bakiri Y, Grandes P, Manzoni OJ (2007) Molecular components and functions of the endocannabinoid system in mouse prefrontal cortex. PLoS ONE 2:e709
106. Bruchey AK, Shumake J, Gonzalez-Lima F (2007) Network model of fear extinction and renewal functional pathways. Neuroscience 145:423–437
107. Siegmund A, Wotjak CT (2007) A mouse model of posttraumatic stress disorder that distinguishes between conditioned and sensitised fear. J Psychiatr Res 41:848–860