Fatty Acid Amide Hydrolase (−/−) Mice Exhibit an Increased Sensitivity to the Disruptive Effects of Anandamide or Oleamide in a Working Memory Water Maze Task

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ABSTRACT

Although recent evidence suggests that fatty acid amide hydrolase (FAAH) may represent a potential therapeutic target, few published studies have investigated FAAH or its fatty acid amide substrates (FAAs) in animal models of learning and memory. Therefore, our primary goal was to determine whether FAAH (−/−) mice, which possess elevated levels of anandamide and other FAAs, would display altered performance in four Morris water maze tasks: acquisition of a hidden fixed platform, reversal learning, working memory, and probe trials. FAAH (−/−) mice failed to exhibit deficits in any task; in fact, they initially acquired the working memory task more rapidly than FAAH (+/+ ) mice. The second goal of this study was to investigate whether the FAAH inhibitor OL-135 (1-oxo-1[5-(2-pyridyl)-2-yl]-7-phenylheptane), anandamide, other FAAs, and methanandamide would affect working memory in both genotypes. FAAH (−/−), but not (+/+), mice displayed working memory impairments following exogenous administration of anandamide (ED50 = 6 mg/kg) or oleamide (50 mg/kg). However, the central cannabinoid receptor (CB1) receptor antagonist SR141716 [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide HCl] only blocked the disruptive effects of anandamide. Methanandamide, which is not metabolized by FAAH, disrupted working memory performance in both genotypes (ED50 = 10 mg/kg), suggesting that CB1 receptor signaling is unaltered by FAAH deletion. In contrast, OL-135 and other FAAs failed to affect working memory in either genotype. These results suggest that FAAH deletion does not impair spatial learning but may enhance acquisition under certain conditions. More generally, FAAH may represent a novel therapeutic target that circumvents the undesirable cognitive side effects commonly associated with direct-acting cannabinoid agonists.
cb1 cannabinoid because they are blocked by cb1 antagonists and do not occur in cb1 receptors. however, exogenous administration of an agonist cannot be expected to mimic closely the actions of an endogenous system tightly integrated within neural circuits sensitive to specific spatiotemporal contexts.

the first objective of the present study was to determine whether deletion of faah would result in a phenotype that is reminiscent of the pharmacological effects of cannabinoid agonists in morris water maze tasks. specifically, we assessed faah (+/−) and (+/+) mice for acquisition in a reference memory (i.e., a standard hidden, fixed platform) task, performance in a reversal test, acquisition of a working memory (i.e., repeated acquisition) task, and performance in a cued task in which the platform is made visible to assess sensorimotor or motivational deficits.

our second major objective was to evaluate whether faah (+/−) mice would exhibit an increased sensitivity to the memory-disruptive effects of anandamide and other faas (i.e., oleamide, opea, and oea) in the working memory task. a two-trial repeated acquisition task was chosen to evaluate this hypothesis because we have shown previously that this task is more sensitive to disruption by cannabinoid agonists as well as by scopolamine than the fixed platform (i.e., reference memory) and cued water maze procedures (varvel et al., 2001). in addition, mice were treated with methanandamide as a positive control because this synthetic analog is not metabolized by faah, and we have demonstrated previously that it produces a cb1-mediated disruption in the working memory morris water maze task (varvel and lightman, 2002).

containing increased slow-wave sleep (huitron-resendiz et al., 2004). despite a growing consensus that the endocannabinoid system modulates cognition, little is known about the role of faah in the regulation of learning and memory.

one issue related to elevating levels of anandamide via faah inhibition that has not yet been addressed is whether spatial learning processes are disrupted in a manner similar to what has been observed following exogenous administration of cannabinoid agonists. it has long been recognized that marijuana and its chief psychoactive component, Δ9-tetrahydrocannabinol (thc), produce disturbances in various aspects of learning and memory of humans (chait and pierri, 1992) and in animal models of learning and memory. specifically, cannabinoid agonists at doses that do not produce many commonly assessed cannabinoid effects (e.g., hypomotility, analgesia, catalepsy, and hypothermia) selectively disrupt tasks heavily dependent on working memory (i.e., short term), but not reference (i.e., long term), memory as assessed in a variety of operant and spatial paradigms (heyser et al., 1993; mallet and beninger, 1996; jentsch et al., 1997; varvel et al., 2001). these effects have been shown to be mediated via the cb1 receptor because they are blocked by cb1 antagonists and do not occur in cb1 (−/−) mice (heyser et al., 1993; mallet and beninger, 1998; varvel and lightman, 2002). however, exogenous administration of an agonist cannot be expected to mimic closely the actions of an endogenous system tightly integrated within neural circuits sensitive to specific spatiotemporal contexts.

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materials and methods

subjects. male faah (+/+) and (−/−) mice used in this study were 6th generation backcrossed onto a c57bl/6 background as previously described (lichtman et al., 2004). all subjects weighed between 20 and 30 g and were housed five animals per cage in a temperature-controlled (20–22°C) facility. mice were approximately 8 weeks of age at the beginning of training and were less than 52 weeks of age by the conclusion of the study. the institutional animal care and use committee at virginia commonwealth university approved all experiments. food and water were available ad libitum in the home cages. all experiments were approved by the institutional animal care and use committee at virginia commonwealth university.

apparatus. the water maze consisted of a large circular galvanized steel pool (1.8-m diameter, 0.6-m height) surrounded by curtains displaying large, high-contrast geometric shapes that remained in a consistent orientation throughout the study. a white platform (10-cm diameter) was placed inside, and the tank was filled with water (22°C) until the top of the platform was submerged 1 cm below the water’s surface. a sufficient amount of white paint (proline latex flat; martin senour paints, cleveland, oh) was added to make the water opaque and render the platform virtually invisible. an automated tracking system (columbus instruments, columbus, oh) analyzed the swim path of each subject and calculated several corresponding dependent measures: escape latencies (the time between being placed in the water and finding the hidden platform), total path lengths (the total distance traveled between being placed in the pool and finding the platform), average swim speeds, degree of thigmotaxia (percentage of time spent in periphery of the pool), percentage of time spent in the target quadrant, and the number of entries into specified target areas.

drugs. anandamide and sr141716 were provided by the national institute on drug abuse (bethesda, md); methanandamide (man) was purchased from tocris (ballwin, mo); oleamide, opea, and oea were purchased from cayman chemical (ann arbor, mi); and ol-135 was synthesized according to boger et al. (2005). all drugs were dissolved in a 1:1 mixture of absolute ethanol and alkaloids-620 (rhone-poulenc, princeton, nj) and diluted with saline to a final ratio of 1:1.18 (ethanol/alkaloids/saline). drug injections were administered s.c. in an injection volume of 10 ml/kg.

procedure. the initial experiment was designed to evaluate the ability of faah knockout (n = 8) and wild-type (n = 6) mice to acquire a fixed platform water maze task. acquisition procedures were identical to those described previously (varvel et al., 2001). before acquisition training, each subject was given a single 5-min acclimation trial in which it was placed in the tank with no platform present. mice then received eight acquisition sessions in which the hidden platform remained in a fixed location, with each session consisting of four 2-min trials separated by approximately 10 min (4 or 5 days per week). after completion of the acquisition training, the platform was moved to the opposite side of the tank, and the ability of mice to acquire the new location (i.e., a reversal task) was assessed. other than the location of the platform, procedures for the reversal test were identical to the acquisition training.

the next series of experiments were conducted to determine whether several substrates of faah, specifically anandamide, oleamide, opea, or oea, produced selective disruptions in a model of working memory (i.e., repeated acquisition). in brief, the platform was moved each day to one of 24 possible positions, with the exact platform position on any given day being randomly determined (positions along the perimeter of the tank and in the exact center were excluded). if a mouse failed to locate the platform during the first trial (trials were 120 s), it was manually guided to it. subsequent trials began after a period of 30 s on the platform, with the mouse released into the water from the same position as the first trial (first trial start positions were randomly determined). training criteria were set so that subjects were required to locate the platform in less than
30 s on two of three trials subsequent to the first trial and were required to maintain this level of performance on three of their four most recent training sessions before initiating drug testing. Because we have previously found that some mice that initially met training criteria can begin to exhibit erratic performance (unpublished observations), any mouse from the study that failed to perform well on five consecutive training sessions was removed from the study. Drug tests were conducted identically to training sessions except that only two 120-s trials were given, and test sessions were spaced at least 72 h apart (with at least one intervening training session) to ensure drug clearance. The order of the drugs tested was AEA, MAN, OLE, OL-135, PEA, and OEA, with individual doses of a drug counterbalanced with vehicle.

The general strategy for assessing these compounds was to test a high dose of each compound (Lichtman et al., 2002) in each genotype. If a significant disruption of working memory performance was observed, a dose-response experiment was then conducted. Furthermore, pretreatment with 3 mg/kg SR141716 was used to determine the involvement of CB1 receptors. We have previously found that 3 mg/kg SR141716 was the lowest dose of SR141716 that significantly antagonized Δ9-THC-induced impairment in the Morris water maze (Varvel et al., 2001). Finally, drugs that significantly disrupted performance were evaluated in a cued version of this task to identify sensorimotor or motivational deficits. This cued version of the task was similar to the working memory task except that the location of the platform was made known to the mice by placing a black rubber stopper (height, 3 cm; radius, 1.5 cm) on the platform that extended about 2 cm above the surface of the water.

Statistical Analysis. Acquisition and reversal experiments were analyzed with two-way ANOVAs (genotype by session). The primary dependent measure used to assess working memory performance was the savings ratio, calculated as the latency of the first (sample) trial divided by the sum of the latencies of the first and second trials. Thus, a ratio of 0.5 indicates no difference between the trials, whereas higher ratios indicate the degree to which mice found the platform more quickly during the second trial compared with the first trial. These savings ratios were transformed into a percentage scale (the upper limit was that group’s vehicle performance, the lower limit was 0.5) and used to calculate ED50 values with 95% confidence intervals for the group by the method of least-squares linear regression. In the cases where different doses where assessed in each genotype (i.e., AEA, OLE), one-way ANOVAs (Student’s t tests when only a single dose was assessed) were used to evaluate the effects of dose on savings ratios and swim speeds for each genotype. In the cases where the same doses were assessed in both genotypes (MAN, PEA, OEA, OL-135), two-way (drug by genotype) ANOVAs were employed. For all analyses, results were considered statistically significant when \( p < 0.05 \).

Results

Comparison between FAAH (−/−) and (+/+ ) Mice in Morris Water Maze Tasks. No differences were detected between FAAH (+/+ ) and (−/−) mice in the acquisition of the initial fixed-platform learning task or the reversal task. As shown in Fig. 1, A and B, there were no effects of genotype on escape latency \([F(1,84) = 0.05, p = 0.83]\) or path length \([F(1,84) = 0.54, p = 0.48]\) during the initial acquisition. There were also no effects of genotype on swim speeds (data not shown) \([F(1,84) = 0.68, p = 0.43]\). Similarly, no genotype differences were observed in the reversal task as assessed by escape latency \([F(1,44) = 0.03, p = 0.87]\) or the number of times mice returned to the original platform location \([F(1,44) = 0.70, p = 0.42]\).

Escape latencies from the first three working memory sessions are presented in Fig. 2A. Surprisingly, FAAH (−/−) mice actually performed better than FAAH (+/+ ) mice on the first working memory session, as assessed by differences in escape latencies across the three trials \([F(1,22) = 5.1, p < 0.05]\). However, both genotypes performed equally as well on subsequent training sessions because there were no effects of genotype on the second \([F(1,22) = 1.3, p = 0.28]\) or third \([F(1,22) = 0.21, p = 0.65]\) training sessions. As shown in Fig. 2B, FAAH (−/−) mice tended to return to the previous platform location (i.e., the reversal location) less often than did FAAH (+/+ ) mice on the first working memory training session, although this effect just failed to achieve statistical significance \([F(1,22) = 4.2, p = 0.06]\). As described above, mice were required to meet training criteria before drug
testing was initiated. As shown in Fig. 2C, the number of working memory sessions required to meet criteria did not differ between FAAH (+/+) and (−/−) mice [t(11) = 1.0, p = 0.34].

**Pharmacological Treatments to FAAH (−/−) and (+/+) Mice.** During the course of subsequent drug testing, three FAAH (−/−) mice and two FAAH (+/+) mice were excluded from the study because of poor performance. An additional four FAAH (−/−) mice and four FAAH (+/+) mice were trained as described under Materials and Methods (excluding the reversal procedure) and included in the study to achieve appropriate sample sizes for each tested drug. Notably, drugs were not tested in the same order for these mice as in the original group. However, comparable results were achieved, suggesting a lack of any order effects.

As shown in Fig. 3 and Table 1, exogenous AEA administration produced a dose-dependent disruption of working memory performance in FAAH (−/−) mice [ED50 (95% confidence interval) value = 5.8 (3.1–10.7) mg/kg] but failed to impair working memory in the FAAH (+/+) mouse. In FAAH (−/−) mice, AEA reduced the savings ratio (Fig. 3A; F = 3.2, p < 0.05), with lower ratios following 10 and 20 mg/kg AEA than the vehicle ratio (p < 0.05). SR141716 reversed the working memory deficits in the FAAH (−/−) mice [t(7) = 9.9, p < 0.001]. Average swim speeds (Fig. 3B) were also affected in the FAAH (−/−) mice [F(3, 21) = 3.3, p < 0.05], with decreases observed at 20 mg/kg (p < 0.05). Swim speed following the combination of SR141716 + 20 mg/kg AEA was not different from AEA alone [t(7) = 1.8, p = 0.11], although it was no longer different from vehicle [t(7) = 0.54, p = 0.61]. AEA (20 mg/kg) did not affect working memory performance [t(6) = 0.97, p = 0.37] or swim speeds [t(6) = 2.1, p = 0.08] of the FAAH (+/+) mice. Representative swim traces from both genotypes administered vehicle, 20 mg/kg AEA, 20 mg/kg MAN, or 50 mg/kg OLE are presented in Fig. 4.

Figure 5 and Table 1 show the effects of MAN in the working memory task. Analysis of the savings ratio data (Fig. 5A) revealed effects of dose [F(3, 27) = 8.2, p < 0.001] but no difference between the genotypes [F(1, 27) = 0.51, p = 0.49]. Post hoc tests showed that with genotypes combined, savings ratios were reduced following 10 and 20 mg/kg MAN compared with vehicle (p < 0.05). MAN was equipotent in both genotypes because the ED50 (95% confidence interval) values for each genotype were nearly identical, 9.3 (6.9–12.5) and 10.1 (5.0–20.4) mg/kg for FAAH (−/−) and (+/+) mice, respectively. There were no effects of dose [F(3, 27) = 1.9, p = 0.16] or genotype [F(1, 27) = 1.2, p = 0.31] on swim speeds (Fig. 5B).

As shown in Fig. 6A and Table 1, OLE disrupted performance of the FAAH (−/−) mice in the working memory task, as evidenced by the savings ratio data [F(3, 12) = 7.7, p < 0.01], which was different between vehicle and 50 mg/kg (p < 0.01). Swim speeds were also disrupted in the FAAH (−/−) mice at 50 mg/kg [F(3, 12) = 3.9, p < 0.05, Fig. 6B]. Pretreatment with 3 mg/kg SR141716 failed to block the disruptive effect of 50 mg/kg OLE on either savings ratio [t(4) = 0.59, p = 0.59] or swim speed [t(4) = 0.56, p = 0.60]. In contrast, the savings ratios of wild-type mice were unaffected by 50 mg/kg OLE [t(5) = 0.73, p = 0.50], although swim speeds were reduced by this dose [t(5) = 3.0, p < 0.05].

**TABLE 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>FAAH (+/+)</th>
<th>FAAH (−/−)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trial 1</td>
<td>Trial 2</td>
</tr>
<tr>
<td>Anandamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>59.4 (11.5)</td>
<td>17.1 (4.0)</td>
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<tr>
<td>5 mg/kg</td>
<td></td>
<td></td>
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<tr>
<td>10 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>44.1 (10.1)</td>
<td>21.9 (8.9)</td>
</tr>
<tr>
<td>20 + 3 mg/kg SR141716</td>
<td></td>
<td></td>
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<tr>
<td>Methanandamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>55.0 (13.1)</td>
<td>23.2 (10.1)</td>
</tr>
<tr>
<td>5 mg/kg</td>
<td></td>
<td></td>
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<tr>
<td>10 mg/kg</td>
<td></td>
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</tr>
<tr>
<td>20 mg/kg</td>
<td>35.5 (7.2)</td>
<td>38.4 (12.9)</td>
</tr>
<tr>
<td>Oleamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>66.0 (18.0)</td>
<td>21.5 (5.4)</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td></td>
<td></td>
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<tr>
<td>25 mg/kg</td>
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</tr>
<tr>
<td>50 mg/kg</td>
<td>46.6 (13.6)</td>
<td>26.0 (6.0)</td>
</tr>
<tr>
<td>50 + 3 mg/kg SR141716</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>35.4 (7.1)</td>
<td>12.6 (4.3)</td>
</tr>
<tr>
<td>50 mg/kg PEA</td>
<td>51.1 (9.7)</td>
<td>15.3 (3.6)</td>
</tr>
<tr>
<td>50 mg/kg OEA</td>
<td>67.8 (13.8)</td>
<td>38.5 (9.0)</td>
</tr>
<tr>
<td>30 mg/kg OL-135</td>
<td>56.7 (15.3)</td>
<td>12.4 (4.0)</td>
</tr>
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</table>

*Fig. 3.* Anandamide impairs working memory performance in FAAH (−/−) mice (n = 8) through a CB1 receptor mechanism of action but has no effect in FAAH (+/+) mice (n = 7). A, savings ratios were calculated from escape latency data (trial 1/trial 1 + trial 2). B, average swim speeds. *, significant differences compared with vehicle (p < 0.05); †, significant difference between 3 mg/kg SR141716 + 20 mg/kg AEA compared with 20 mg/kg AEA alone (p < 0.05).
The lack of effects of a high dose (50 mg/kg) of the FAAs PEA and OEA on working memory performance is presented in Fig. 7 and Table 1. In addition, the FAAH inhibitor OL-135 (30 mg/kg) failed to alter performance of either genotype in the working memory task. No effects of drug treatment [(3,44)\(p = 0.13\)] or genotype [(1,44)\(p = 0.37\)] on savings ratios (Fig. 7A) were found with a two-way ANOVA. However, swim speeds were affected by drug treatment [(3,44) = 5.6, \(p < 0.01\)], which planned comparisons revealed was due to a decrease following 50 mg/kg OEA (Fig. 7B). There were no main effects of genotype on swim speeds [(1,44) = 0.74, \(p = 0.39\)].

Results of doses of AEA, MAN, and OLE, which disrupted working memory performance, in the cued platform experiment are shown in Fig. 8. As shown in Fig. 8A, no group effects were found for escape latencies [(5,30) = 1.4, \(p = 0.30\)]. However, there were group differences for swim speeds [(3,20) = 5.2, \(p < 0.01\)], where 50 mg/kg OLE reduced speeds compared with vehicle in FAAH (−/−) mice (\(p < 0.01\), Fig. 8B).

Discussion

FAAH (−/−) mice displayed normal phenotypes in their ability to acquire the fixed-platform, reversal, and working memory tasks, despite possessing approximately 10-fold elevated brain levels of anandamide (Cravatt et al., 2001). These results stand in contrast to direct-acting cannabinoid agonists, which have been shown to impair acquisition in fixed-platform water maze tasks (Ferrari et al., 1999; da Silva and Takahashi, 2002), as well as to produce CB1-mediated deficits in performance of the same working memory procedure used here (Varvel and Lichtman, 2002). Unexpectedly, FAAH (−/−) mice performed better than FAAH (+/+ +) mice during the first working memory training session (see Fig. 2A). However, the observations that no genotype differences were observed either upon subsequent training days or on vehicle test days preclude claims of cognitive enhancement. Indeed, the anxiolytic effects produced by the FAAH inhibitor URB597 (Kathuria et al., 2003) may account for the subtle genotype difference found here. The absence of learning impairments suggests that the elevated levels of anandamide and other FAAs seen in FAAH (−/−) mice may either have failed to achieve sufficient concentrations at the appropriate sites to disrupt learning or exerted qualitatively different effects on specific neurochemical pathways compared with those elicited by cannabinoid agonists.

These results highlight an important difference between in vivo effects of FAAH inhibition and cannabinoid agonists. We have reported previously that THC is more potent at disrupting working memory performance than at producing analgesia or other commonly assessed effects of THC (Varvel et al., 2001). However, FAAH (−/−) mice or OL-135-treated mice failed to exhibit any disruption in working memory perfor-
In the other direction because FAAH activity was up-regulated, it is possible that a putative cognitive-enhancing anandamide-induced deficit. For example, oleamide was reported to protect mice from scopolamine-induced deficits in passive avoidance and Y-maze tests, presumably via activating choline acetyltransferase (Heo et al., 2003).

Our second major objective was to evaluate whether FAAH (-/-) mice exhibited an increased sensitivity to the memory-disruptive effects of anandamide and other FAAs compared with FAAH (+/+) mice. Most notably, anandamide produced dose-dependent disruptions of working memory performance in the FAAH (-/-) mice but had no apparent effects in FAAH (+/+) mice. Importantly, the ability of FAAH (-/-) mice to swim to the platform in the cued task in which the platform was made visible (see Fig. 8A) argues against an interpretation based solely on sensorimotor or motivational effects. Anandamide-induced working memory impairment was mediated by CB1 receptor mechanism of action because SR141716 reversed this effect (see Fig. 3A). In earlier studies, anandamide failed to impair memory (Lichtman et al., 1995; Brodkin and Moerschbaecher, 1997), most likely due to its rapid degradation (Willoughby et al., 1997). However, the nonspecific amidase inhibitor phenylmethylsulfonyl fluoride enabled anandamide to produce selective working memory deficits in a two-component operant task, which were reversed by SR141716 (Mallet and Beninger, 1998). In contrast, we report here that methanandamide produced working deficits that were independent of FAAH and have reported previously that methanandamide-induced memory impairment was blocked by SR141716 and failed to occur in CB1 (-/-) mice (Varvel and Lichtman, 2002). As discussed above, the observation that methanandamide was equipotent in both genotypes further suggests that deletion of FAAH does not alter CB1 function.

In addition to exhibiting an increased sensitivity to the exogenous effects of anandamide in the water maze, FAAH (-/-) mice also exhibited an increased sensitivity to the disruptive effects of oleamide on performance in the working memory task but not in the cued task. These findings taken together are consistent with the notion that oleamide elicited a specific working memory deficit in FAAH (-/-) mice, irrespective of the reductions in swim speed it produced in both genotypes. Importantly, none of oleamide's effects were blocked by SR141716, indicating a non-CB1 receptor mechanism of action. Similarly, we have reported previously that SR141716 failed to block the hypothermic, hypoactive, and ptosis effects of oleamide (Lichtman et al., 2002). Although oleamide has been reported to disrupt theta-burst long-term potentiation, but not high-frequency stimulation long-term potentiation, through a non-CB1 mechanism that may involve modulation of GABAergic transmission (Lees and Dourakis, 2004), its direct molecular targets are currently unknown.

Both PEA and OEA seem to possess little propensity for undesirable cognitive side effects because even large doses administered to FAAH (-/-) mice failed to elicit working memory deficits (see Fig. 7A). In comparison, antiinflammatory and analgesic effects of PEA occur at lower doses (Jaggar et al., 1998) than the 50 mg/kg dose used here. OEA, which is involved in the regulation of feeding behaviors via its activity at peroxisome proliferator-activated receptor α (Lo Verme et al., 2005), also produced no spatial learning impairments at 50 mg/kg, even though decreases in swim speed were evident. This dose of OEA was previously shown to decrease locomotor activity and produce mild ptosis in FAAH (-/-) and (+/+) mice (Lichtman et al., 2002).

In conclusion, anandamide selectively disrupted working memory in FAAH (-/-) mice but had no apparent effects in FAAH (+/+) mice. These findings are consistent with those...
of previous studies indicating that FAAH (−/−) mice exhibit supersensitivity to the pharmacological effects of exogenously administered anandamide (Cravatt et al., 2001). In contrast, the observation that the FAAH-resistant cannabinoid analog methanandamide was equipotent in disrupting working memory in both genotypes indicates normal functioning of CB1 receptors in FAAH (−/−) mice. In addition, FAAH (−/−) mice exhibited an increased sensitivity to the memory-disruptive effects of oleamide through a non-CB1 receptor mechanism of action. Most importantly, genetic deletion of FAAH failed to elicit spatial learning deficits as assessed in several variations of the water maze, and a behaviorally active dose of the FAAH inhibitor OL-135 did not produce working memory impairments. However, it is unknown whether FAAH (−/−) mice will exhibit deficits in other learning and memory tasks. The observations that disruption of CB1 signaling impairs extinction learning in conditioned freezing (Marsicano et al., 2002; Suzuki et al., 2004) and Morris water maze (Varvel et al., 2005) tasks suggest that genetic deletion or pharmacological inhibition of FAAH may facilitate extinction learning. Moreover, the recent report that CB1 (−/−) mice exhibit accelerated age-related deficits in cognitive functioning as well as decreases in the number of CA1 and CA3 hippocampal neurons compared with wild-type mice (Bilkei-Gorzo et al., 2005) raises the intriguing possibility that deletion or inhibition of FAAH may offer protection from cognitive deficits associated with old age. Taken together, the present results suggest that increasing endogenous levels of anandamide and other FAAHs does not impair working or reference memory in the Morris water maze. Moreover, the development of selective FAAH inhibitors may represent a novel therapeutic approach that circumvents the undesirable cognitive side effects commonly associated with direct-acting cannabinoid agonists.

References

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