**Peroxisome proliferator-activated receptors (PPARs): new target for attention and memory functions**

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**BACKGROUND AND AIM OF THE STUDY**

- FAAH is an enzyme hydrolyzing several bioactive fatty acid ethanolamides, including anandamide (CB1 agonist), and the non-cannabinoids OEA and PEA, which are PPARs agonists (Fu et al., 2003), and FAAH inhibition induces a consistent increase in levels of all these endogenous compounds (Fegley et al., 2005).
- It has been shown that exogenous cannabinoid agonists THC (Vierio et al. 2004; Psychopharmacology 177: 141–150) and WIN 55212-2 (Arguello and Jentsch 2004; Neuropsychopharmacology 29: 522 – 529) can impair attention in rodents. However, the role of the endocannabinoid, anandamide, in attention is not known.
- Furthermore, endocannabinoïd’s involvement in cognition has not been systematically investigated. Here we have evaluated the behavioral effects of pharmacological elevations of these bioactive substances by inhibiting FAAH activity, with URB597.

**MATERIALS AND METHODS**

- Male Sprague-Dawley rats 300-350 gr (Charles River USA)
- URB597 (0.1, 0.3 and 1 mg/kg), dissolved in DMSO 50% sterile water; YY14643 (20 and 40 mg/kg), dissolved in DMSO 70% sterile water; MK886 (0.3 and 1 mg/kg), dissolved in 2% Tween80, 2% ethanol sterile water; Anandamide (3, 10 mg/kg), Rimonabant (SR141716 1 and 3 mg/kg) and THC (1, 3, 5 and 10 mg/kg) were prepared in 2% Tween80, 2% ethanol and sterile water. All drugs were injected intraperitoneally in a volume of 1 ml/kg.
- Behavioral tests: step through passive avoidance, consisting of an adaptation trial (day 1), a learning trial (LT; day 2), and two retention test (RT1 and RT2; day 3 and 9 respectively); attention were assessed using the 5-choice serial reaction-time task (5-CSRTT) using MED-Associates chambers and software.

**RESULTS**

- URB597, given acutely, did not impair performance during the retention tests, in contrast to scopolamine, suggesting that URB597 does not impair learning, consolidation, retrieval or extinction of the aversive stimulus.
- A low dose of URB597 (0.1 mg/kg) produced a small but significant increase in latency to reenter the dark compartment during the second retention test compared to vehicle.
- The positive effects of URB597 on short- and long-term memory, during the first and the second retention tests, were not blocked by the cannabinoid CB1 receptor antagonist SR141716, but it was significantly counteracted by the PPARs antagonist MK886 0.3 and 1 mg/kg.
- A low dose of THC produced a small but significant increase in latency to reenter the dark compartment during the second retention test compared to vehicle.
- Furthermore, the CB1 agonist, THC, had no effect on behavior in the attention task in these animals, while anandamide alone on omissions was even more effective than the CB1 antagonist, rimonabant.
- Furthermore, 10 mg/kg anandamide was given in combination with the CB1 antagonist, rimonabant. The combination of 10 mg/kg anandamide with 0.1 mg/kg URB 597 significantly decreased accuracy in the attentional task.
- A low dose of THC produced an increase in omissions that was no longer significant when given alone, and a significant increase in omissions also occurred at the second highest dose of anandamide.
- In addition, the combination of 10 mg/kg anandamide with 0.1 mg/kg URB 597 significantly decreased accuracy in the attentional task.
- Surprisingly, when anandamide was given in combination with a higher dose of URB597 (0.3 mg/kg), increases in omissions were no longer seen. URB 597 alone (had no effect on omissions or accuracy.)
- To determine whether these effects of anandamide were mediated by cannabinoid CB1 receptors, 10 mg/kg anandamide was given in combination with the CB1 antagonist, rimonabant.
- Furthermore, the CB1 agonist THC had no effect on behavior in the attention task in these animals. During this phase of the study, the effects of anandamide alone on omissions was even greater than in the original determination.