IMPROVEMENTS IN LONG-TERM MEMORY RETENTION BY INHIBITION OF FATTY ACID AMIDE HYDROLASE (FAAH) ARE MEDIATED BY A-TYPE PEROXISONE PROLIFERATOR-ACTIVATED RECEPTORS (PPARA) AND NOT BY CANNABINOID CB_1 RECEPTORS

Mazzola C[1], , Medalie J[1], Panlilio LV[1], Solinas M[2], Drago F[3], Goldberg SR[1] and Yasar S[4]

[1] Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch, Intramural Research Program, NIDA, NIH, DHHS, Baltimore, MD, 21224, USA.[2] Department Laboratoire de Biologie et Physiologie Cellulaires, CNRS-6187, Université de Poitiers, 86022, Poitiers, France. [3] Department of Experimental and Clinical Pharmacology, Medical School, University of Catania, Italy. [4] Division of Geriatric Medicine, Johns Hopkins Medical School, Baltimore, MD, 21224, USA

Fatty acid amide hydrolase (FAAH) is an intracellular enzyme catalyzing hydrolysis of endogenous lipid mediators, such as anandamide (an endogenous cannabinoid CB1 receptor agonist), as well as oleoyethanolamide (OEA) and palmitoyethanolamide (PEA), which are endogenous agonists for the peroxisone proliferator-activated receptor-α (PPARα). Cyclohexyl carbamic acid 3'-carbamoyl-3-yl ester (URB597) selectively inhibits intracellular FAAH activity, resulting in increased levels of anandamide, OEA and PEA in several brain areas, incliding regions mediating learning and memory. Here we studied effects of FAAH inhibition and PPARα activation on learning and memory using a passive-avoidance task in rats. During a single learning trial, rats were placed in the lighted compartment of a shuttle box, and received foot shocks when they entered the dark compartment. URB597 (0.1, 0.3 or 1.0 mg/kg) was given i.p. 40 min before the learning trial. During a retention test 24 hr later (short-term memory), rats that had received 0.1 mg/kg URB597, but not 0.3 or 1 mg/kg, before the learning trial showed small but significant increases in latency to enter the dark compartment, indicating improvements in learning by FAAH inhibition. During a second retention trial 7 days later (long-term memory), rats that had received all three doses of URB597 before the learning trial showed marked and significant increases in latency to enter the dark compartment. This effect of URB597 on long-term memory retention was not blocked by the CB1 receptor antagonist SR141716 (1 or 3 mg/kg, i.p., 1 h before the learning trial), but was blocked by the PPARα antagonist MK886 (1 mg/kg, i.p., 1 h before the learning trial). When the synthetic PPARα agonist WY14643 (40 mg/kg) was given i.p. 10 min before the learning trial, the latency to enter the dark compartment during the 7-day retention test was also markedly and significantly increased and this effect was reversed by MK886. These results suggest that improvements in long-term memory retention produced by FAAH inhibition are not cannabinoid-receptor dependent and, instead, are mediated by PPARα activation. Supported by the Intramural Research program of NIDA, NIH, DHHS.