THE FATTY-ACID AMIDE HYDROLASE INHIBITOR URB597 REDUCES NEUROPATHIC PAIN AFTER ORAL ADMINISTRATION IN MICE

Roberto Russo, Giovanna La Rana, Giuseppe D'Agostino, Oscar Sasso, Jesse LoVerme, Daniele Piomelli and Antonio Calignano

Department of Experimental Pharmacology, University of Naples, Italy.
Department of Pharmacology and the Center for Drug Discovery, University of California, Irvine

Fatty-acid amide hydrolase (FAAH) is an intracellular serine hydrolase that catalyzes the cleavage of bioactive fatty-acid ethanolamides such as anandamide and palmitoyethanolamide (PEA) (1). Genetic deletion of the *faah* gene in mice elevates brain anandamide levels and amplifies the antinociceptive effects of this endogenous cannabinoid agonist (2). Similarly, pharmacological blockade of FAAH activity reduces nocifensive behavior in animal models of acute and inflammatory pain (3-4). In the present study, we investigated the effects of the selective FAAH inhibitor URB597 (cyclohexyl carbamic acid 3'-carbamoyl-biphenyl-3-yl ester) in the mouse chronic constriction injury (CCI) model of neuropathic pain. Oral administration of URB597 (1-50 $mg\text{-}kg^{-1}$, once daily) for 4 days produced a dose-dependent reduction in nocifensive responses to thermal and mechanical stimuli, which was prevented by a single intraperitoneal (i.p.) administration of the cannabinoid CB_1 receptor antagonist rimonabant (1 $mg\text{-}kg^{-1}$). The antihyperalgesic effects of URB597 were accompanied by a reduction in plasma extravasation in the ligated paws, which was also sensitive to rimonabant (1 $mg\text{-}kg^{-1}$, i.p.) and partially reversed by the CB_2 antagonist SR144528 (1 $mg\text{-}kg^{-1}$, i.p.). Oral dosing with URB597 achieved significant albeit transient levels of this drug in plasma, inhibited brain FAAH activity and elevated spinal cord anandamide and PEA levels. The results provide new evidence for a role of the endocannabinoid system in pain modulation and reinforce the proposed role of FAAH as a target for analgesic drug development.

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