EFFECT OF THE SELECTIVE FATTY ACID AMIDE HYDROLASE INHIBITOR URB597 ON ETHANOL ABUSE RELATED BEHAVIOURS IN THE RAT

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The endocannabinoid system is involved in the regulation of various aspects of alcohol related behaviour. For instance, treatment with selective CB1 receptor antagonists reduces ethanol intake and conditioned reinstatement of ethanol seeking, whereas CB1 receptor agonists facilitate alcohol drinking. URB597 is a potent, selective and systemically active inhibitor of fatty acid amide hydrolase (FAAH) that, following peripheral administration, increases anandamide levels in the brain and potentiates anandamides' effects enhancing CB1 receptor activation. Here, we studied the effect of URB597 on alcohol self-administration, on stress- and cue-induced reinstatement of alcohol seeking. Wistar rats were trained to operantly self-administer 10% ethanol until stable baseline of responding was established. At this point, rats were treated with URB597 (0.0, 0.1, 0.3, 1.0 mg/kg) 30 min prior to the self-administration session. Results showed no effect of drug ($P>0.05$). An additional test carried out under progressive ratio schedule of reinforcement showed that URB597 did not modify the break point for ethanol responding ($p>0.05$). In a subsequent series of experiments the ability of URB597 to modulate reinstatement of alcohol seeking induced by environmental conditioning factors, stress or yohimbine (an anxiogenic drug) was tested. For conditioned reinstatement Wistar rats were trained to self-administer 10% ethanol or water in 30 min daily session on a FR-1. Ethanol availability was signalled by orange odour (S^+) that served as a discriminative stimulus and the activation of the house light for 1 s (CS^+) contingent to each lever pressing. For water, anise odour (S^-) and 1 s white noise (CS^-) were used. Discrimination was followed by an extinction phase during which lever presses did not result in the delivery of ethanol, water or presentation of the corresponding cues. After 15 extinction sessions animal responding was below 10. Re-exposure to the alcohol cues (S^+/CS^+) but not water cues (S^-/CS^-) reinstated responding ($p<0.01$). Treatment with URB597 (0.0, 0.1, 0.3, 1.0 mg/kg) did not modify cue effects. For stress-induced relapse, after acquisition of ethanol self-administration animals were subjected to an extinction phase (15 days) and then tested for stress- (15 min intermittent foot shock) induced reinstatement. Stress elicited a significant reinstatement of ethanol seeking ($p<0.01$) that was not modified by URB597. Similarly, yohimbine (0.125 mg/kg) given under extinction condition elicited a significant reinstatement of responding that was not affected by URB597. These data demonstrates that, contrary to the effect observed following direct activation of CB1 receptors with agonists, increase in CB1 receptor activity consequent to FAAH inhibition does not facilitate alcohol abuse vulnerability.