Amygdaloid Endocannabinoid System modulates alcohol-related behaviors in msP rats

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Over the decades the endocannabinoid system has been implicated in addictive behavior and in the mechanism of action of several drugs of abuse. Several lines of evidence suggested a role of brain endocannabinoid system in the neural circuitry regulating alcohol abuse in different rodent models (Cippitelli et al., 2007; Basavarajappa BS1 et al., 2007).
The discovery of anandamide, a natural lipid ligand for CB1 receptors and of the mechanisms for its biosynthesis and inactivation, have inspired pharmacological strategies to augment endogenous cannabinoid activity in specific brain areas (Cippitelli et al., 2008).
Fatty acid amide hydrolase (FAAH) is a key membrane protein for metabolism of endocannabinoids, including anandamide. The blockade of FAAH activity increases the level of anandamide in the brain, and exhibits superior selectivity in the elicited behavioral effects compared with the treatment with direct CB1 agonists. URB?597 is an irreversible inhibitor of FAAH considered as a potential therapeutic agent in anxiety, depression and pain (Piomelli et al., 2006).
To determine if FAAH regulates ethanol consumption, we investigated whether activation of the endogenous cannabinoid tone by URB597 injection in central (CeA) and basolateral (BLA) amygdala modifies alcohol self-administration in genetically selected Marchigian Sardinian alcohol-preferring (msP) rats, an animal model in which genetic selection for high alcohol preference has led to co-segregation of elevated behavioral sensitivity to stress and anxiety.
Under our experimental condition, administration of URB597 (0.01, 0.3 and 1.0 μg/rat) reduced alcohol self-administration in msP both in CeA and in BLA.
We therefore hypothesize that exogenous administration of URB597, enhancing the endocannabinoid signaling might have attenuated the hyperactivity of the CRF1 R system brain areas analyzed in this study. This might have reduced the negative affective state of msP rats resulting in the attenuation of their drinking.
Physical restraint in rodents is widely used to investigate neurobiological readaptations and pathological conditions associated with stress exposure. Thus, in this study, we evaluated the anxiety-like response to restraint stress after URB597 microinjection into the CeA in msP rats.
Intra-CeA injections of URB597 (1.0 μg/rat) significantly reduced anxiety-like behavior in restraint rats in the elevated plus maze paradigm. The major finding of the present study is the demonstration that the increase of endocannabinoid tone associated with selective inhibition of FAAH in the CeA leads to a reduction of ethanol consumption and attenuate stress-induced anxiety in the rat.

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