CHRONIC ETHANOL INDUCES MORPHOLOGICAL CHANGES ON HIPPOCAMPAL MICROGLIA, WHICH ARE REVERTED BY PHARMACOLOGICAL BLOCKADE OF FAAH WITH URB597

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It is known that morphological changes of microglia over the course of neuroinflammation are tightly coupled to their function. However, ethanol-related microglial morphology is poorly characterized, and their potential throwback by endocannabinoids signalling has not been addressed. Here, we evaluated the pharmacological effects of fatty-acid amide-hydrolase (FAAH) inhibitor URB597 (0.3 mg/kg), oleoylethanolamide (OEA, 10 mg/kg), arachidonylethanolamide (AEA, 10 mg/kg), the CB1 receptor agonist ACEA (3 mg/kg) and the CB2 receptor agonist JWH133 (0.2 mg/kg) administered for 5 days in a rat model of sub-chronic (2 weeks) ethanol diet (11% v/v) exposure. As a result of these trials, URB597 turned to be the most effective treatment. Contrary to ethanol, URB597 reduced the mRNA levels of Iba-1, Tnfa, IL-6 and monocyte chemoattractant protein-1 (MCP-1/CCL2), as well as the number of cells expressing GFAP or iNOS. Moreover, URB597 effects on hippocampal immune system were accompanied by changes in short and long-term visual recognition memory. These results suggest that FAAH inhibition modulates hippocampal microglial recruitment and activation that can be associated with improved hippocampal-dependent memory despite ethanol exposure.

In parallel, microglial morphometric analysis pointed out significant changes after ethanol exposure, suggesting that microglial cell morphology is closely related to ethanol-induced neuroinflammation. Ethanol provoked changes in fractal dimension, lacunarity, density, roughness, cell area and cell perimeter, which explain a decreased complexity of branches and increased cell surface irregularities. Such changes may represent a chronic activation state of microglia. In addition, ethanol effects on the microglial morphological parameters density and fractal dimension were reverted by URB597. Thus, this FAAH inhibitor was able to counteract the sub-chronic ethanol-induced morphological changes of microglia, resulting in a more compact and increased branch complexity, which apparently relate to a less activated state. Therefore, these morphometric parameters are sensitive and valuable tools to evaluate the chronic activation of microglia by ethanol and its pharmacological blockade.


Palabras clave: Cannabinoids, microglia, morphology.

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