CHRONIC ETHANOL INDUCES MORPOHOLOGICAL 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), arachidonoylethanolamide (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*, *Tnfα*, *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.

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