Fenofibrate (a PPAR-α Agonist) Administered During Ethanol Withdrawal Reverts Ethanol-Induced Astrogliosis and Restores the Levels of Glutamate Transporter in Ethanol-Administered Adolescent Rats

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Abstract
High-ethanol intake induces a neuroinflammatory response, which has been proposed as responsible for the maintenance of chronic ethanol consumption. Neuroinflammation decreases glutamate transporter (GLT-1) expression, increasing levels of glutamate that trigger dopamine release at the corticolimbic reward areas, driving long-term drinking behavior. The activation of peroxisome proliferator-activated receptor alpha (PPARα) by fibrates inhibits neuroinflammation, in models other than ethanol consumption. However, the effect of fibrates on ethanol-induced neuroinflammation has not yet been studied. We previously reported that the administration of fenofibrate to ethanol-drinking rats decreased ethanol consumption. Here, we studied whether fenofibrate effects are related to a decrease in ethanol-induced neuroinflammation and to the normalization of the levels of GLT-1. Rats were administered ethanol on alternate days for 4 weeks (2 g/kg/day). After ethanol withdrawal, fenofibrate was administered for 14 days (50 mg/kg/day) and the levels of glial fibrillary acidic protein (GFAP), phosphorylated NF-κB-inhibitory protein (pIκBα) and GLT-1, were quantified in the prefrontal cortex, hippocampus, and hypothalamus. Ethanol treatment increased the levels of GFAP in the hippocampus and hypothalamus, indicating a clear astrocytic activation. Similarly, ethanol increased the levels of pIκBα in the three areas. The administration of fenofibrate decreased the expression of GFAP and pIκBα in the three areas. These results indicate that fenofibrate reverts both astrogliosis and NF-κB activation. Finally, ethanol decreased GLT-1 expression in the prefrontal cortex and hippocampus. Fenofibrate normalized the levels of GLT-1 in both areas, suggesting that its effect in reducing ethanol consumption could be due to the normalization of glutamatergic tone.

Author keywords
alcohol use disorder
alcoholism
fibrates
neuroinflammation
treatment