Neurodegeneration and cognitive deficits induced by excessive alcohol intake, are prevented by activation of PPARγ

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The excessivealcoholintake is a defining characteristic of analcoholuse disorder (AUD) and leads to serious neurodegenerationand cognitive dysfunctions.Alcohol-induced neurocognitive deficits are associated with activation of oxidative-inflammatory cascade coupled with extensive apoptoticneurodegenerationin different brain regions. Recent findings showed that agonists of PPARγ receptors possess anti-inflammatory and anti-oxidant properties. Starting from these evidences, we evaluated the effect of PPARγ receptor agonist, Pioglitazone, on neuronal death, loss of cognitive flexibility and spatial working memory impairment in a rat model of binge-like exposure to alcohol. Two groups of rats were used. The first one was intoxicated, via repeated intragastric ethanol intubations. Ethanol solution (final concentration 20% w/v) was made up in isocaloric sweet condensed milk and intubated three times per day for 5 consecutive days approximately in a total volume of 20 ml/kg/day. The second group received equivalent volumes of isocaloric sweet condensed milk. Subgroups of rats were concomitantly treated with pioglitazone (0, 30 and 60 mg/kg) twice daily at 12-hrs interval. At the end of the intoxication procedure, animals were sacrificed and neurodegeneration was assessed by Fluoro-Jade B immunostaining. In order to evaluate cognitive functions additional groups of rats were prepared to test the effects of alcohol and pioglitazone on the reversal learning task and in the Morris water maze test. Results showed alcohol-induced neurodegeneration in the hippocampal region of dentate gyrus (DG) and in the adjacent entorhinal cortex (EC). Pioglitazone (60 mg/kg) significantly attenuated alcohol-induced neurodegeneration in these areas. Behavioral tests revealed that alcohol intoxication impaired cognitive flexibility in the reversal learning task and reduced spatial memory and orientation in the Morris water maze test. Treatment with pioglitazone significantly prevented these negative effects of alcohol.

In conclusion our data demonstrated that activation of PPARγ by pioglitazone attenuated alcohol-induced neurodegeneration and rescued memory impairment subsequent to chronic alcohol intoxication.