Activation of melanocortin-4 receptor by a synthetic agonist inhibits ethanolinduced neuroinflammation in rats

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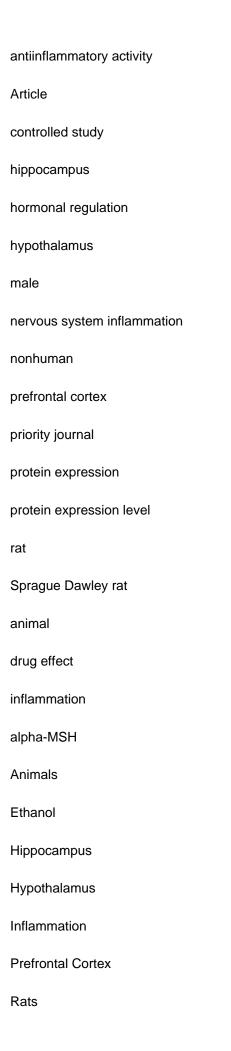
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Background: High ethanol intake induces a neuroinflammatory response resulting in the subsequent maintenance of chronic alcohol consumption. The melanocortin system plays a pivotal role in the modulation of alcohol consumption. Interestingly, it has been shown that the activation of melanocortin-4 receptor (MC4R) in the brain decreases the neuroinflammatory response in models of brain damage other than alcohol consumption, such as LPS-induced neuroinflammation, cerebral ischemia, glutamate excitotoxicity, and spinal cord injury. Objectives: In this work, we aimed to study whether MC4R activation by a synthetic MC4R-agonist peptide prevents ethanol-induced neuroinflammation, and if alcohol consumption produces changes in MC4R expression in the hippocampus and hypothalamus. Methods: Ethanol-preferring Sprague Dawley rats were selected offering access to 20% ethanol on alternate days for 4 weeks (intermittent access protocol). After this time, animals were i.p. administered an MC4R agonist peptide in the last 2 days of the protocol. Then, the expression of the proinflammatory cytokines interleukin 6 (IL-6), interleukin 1-beta (IL-1?), and tumor necrosis factor-alpha (TNF-?) were measured in the hippocampus, hypothalamus and prefrontal cortex. It was also evaluated if ethanol intake produces alterations in the expression of MC4R in the hippocampus and the hypothalamus. Results: Alcohol consumption increased the expression of MC4R in the hippocampus and the hypothalamus. The administration of the MC4R agonist reduced IL-6, IL-1? and TNF-? levels in hippocampus, hypothalamus and prefrontal cortex, to those observed in control rats that did not drink alcohol. Conclusion: High ethanol consumption produces an increase in the expression of MC4R in the hippocampus and hypothalamus. The administration of a synthetic MC4R-agonist peptide prevents neuroinflammation induced by alcohol

consumption in the hippocampus, hypothalamus, and prefrontal cortex. These results could explain the effect of ?-MSH and other synthetic MC4R agonists in decreasing alcohol intake through the reduction of the ethanol-induced inflammatory response in the brain. © 2019 Bentham Science Publishers. Alcohol use disorder Hypothalamus MC4R Melanocortin Neuroinflammation ?-MSH alpha intermedin cyclo(beta alanylhistidyl dextro phenylalanylarginyltryptophanylglutamic acid)amide interleukin 1beta interleukin 6 melanocortin 4 receptor melanocortin receptor agonist tumor necrosis factor unclassified drug alcohol alpha intermedin melanocortin 4 receptor melanocortin receptor type 4, rat alcohol consumption animal experiment animal model animal tissue



Rats, Sprague-Dawley

Receptor, Melanocortin, Type 4