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

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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.

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

antiinflammatory activity

Article

controlled study

hippocampus

hormonal regulation

hypothalamus

male

nervous system inflammation

nonhuman

prefrontal cortex

priority journal

protein expression

protein expression level

rat

Sprague Dawley rat

animal

drug effect

inflammation

alpha-MSH

Animals

Ethanol

Hippocampus

Hypothalamus

Inflammation

Prefrontal Cortex

Rats

Rats, Sprague-Dawley

Receptor, Melanocortin, Type 4