Neuroinflammation produced by heavy alcohol intake is due to loops of interactions between Toll-like 4 and TNF receptors, peroxisome proliferator-activated receptors and the central melanocortin system: A novel hypothesis and new therapeutic avenues

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Excessive alcohol intake induces an inflammatory response in the brain, via TNF?, TLR4 and NF-?B signaling pathways. It has been proposed that neuroinflammation would play a very important role in the development of alcohol addiction. In addition to stimulating the synthesis of inflammatory mediators such as IL-6, IL-1? and TNF?, NF-?B is capable of reducing the anti-inflammatory activity of PPAR? and PPAR?. Reciprocally, PPAR?, PPAR? and melanocortin 4 receptor (MC4R) can decrease the proinflammatory activity of NF-?B, establishing an interplay of inactivations between such nuclear factors and receptors. In this review, we hypothesize that one of the mechanisms by which alcohol produces neuroinflammation is through NF-?B-mediated decrease in PPAR? and PPAR? anti-inflammatory activities; in addition, ethanol negatively affects MC4R activity, decreasing the ability of this receptor to activate PPAR?. PPAR?, PPAR? and MC4R can be pharmacologically activated by synthetic ligands (fibrates, thiazolidinediones and synthetic peptides, respectively); in this context, we propose that the administration of such ligands would decrease neuroinflammation produced by alcohol intake. The advantage of this approach is that fibrates and thiazolidinediones are FDA-approved drugs that have been used for years in other clinical conditions, and now may offer a new perspective for the treatment of alcoholism.

Anti-inflammation

Ethanol intake

MC4R

Melanocortin system

Neuroinflammation

PPAR

TLR4

2,4 thiazolidinedione derivative

alcohol

fibric acid derivative

immunoglobulin enhancer binding protein

melanocortin 4 receptor

peroxisome proliferator activated receptor alpha

peroxisome proliferator activated receptor gamma

synthetic peptide

toll like receptor 4

tumor necrosis factor receptor

alcohol

antiinflammatory agent

ligand

melanocortin

peroxisome proliferator activated receptor

toll like receptor

tumor necrosis factor receptor

alcohol abuse

alcohol consumption

alcoholism

antiinflammatory activity

human

ligand binding

nervous system inflammation

nonhuman

priority journal

protein protein interaction

Short Survey

animal

chemically induced

drinking behavior

inflammation

metabolism

pathophysiology

Alcohol Drinking

Animals

Anti-Inflammatory Agents

Ethanol

Humans

Inflammation

Ligands

Melanocortins

Peroxisome Proliferator-Activated Receptors

Receptors, Tumor Necrosis Factor

Toll-Like Receptors