Ethanol induces microglial cell death via the NOX/ROS/PARP/TRPM2 signalling pathway

ABSTRACT

Microglial cells are the primary immune cell resident in the brain. Growing evidence indicates that microglial cells play a prominent role in alcohol-induced brain pathologies. However, alcohol-induced effects on microglial cells and the underlying mechanisms are not fully understood, and evidence exists to support generation of oxidative stress due to NADPH oxidases (NOX_-mediated production of reactive oxygen species (ROS). Here, we investigated the role of the oxidative stress-sensitive Ca2+-permeable transient receptor potential melastatin-related 2 (TRPM2) channel in ethanol (EtOH)-induced microglial cell death using BV2 microglial cells. Like H2O2, exposure to EtOH induced concentration-dependent cell death, assessed using a propidium iodide assay. H2O2/EtOH-induced cell death was inhibited by treatment with TRPM2 channel inhibitors and also treatment with poly(ADP-ribose) polymerase (PARP) inhibitors, demonstrating the critical role of PARP and the TRPM2 channel in EtOH-induced cell death. Exposure to EtOH, as expected, led to an increase in ROS production, shown using imaging of 2',7'-dichlorofluorescein fluorescence. Consistently, EtOH-induced microglial cell death was suppressed by inhibition of NADPH oxidase (NOX) as well as inhibition of protein kinase C. Taken together, our results suggest that exposure to high doses of ethanol can induce microglial cell death via the NOX/ROS/PARP/TRPM2 signaling pathway, providing novel and potentially important insights into alcohol-induced brain pathologies.

Keyword: Alcoholism; Microglia; Cell death; ROS; Oxidative stress; PARP; TRPM2; NOX