Inhibition of MCP-1/CCR2 signaling offers protection against ethanol-induced damage to the developing brain

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Fetal ethanol exposure may result in fetal alcohol spectrum disorder (FASD) and one of the most devastating effects of developmental exposure to ethanol is the loss of CNS neurons. The underlying molecular mechanisms, however, are unclear. Ethanol-induced neuronal death is accompanied by neuroinflammation. Monocyte Chemoattractant Protein 1 (MCP-1), is a chemokine which is involved in neuroinflammation. Elevated expression of MCP-1 has been observed in multiple sclerosis, stroke and Alzheimer's disease patients. And several mice studies showed the detrimental effects caused by overexpression of MCP-1 in those diseases could be abolished (or partially abolished) by CCR-2 antagonist. We hypothesize that the inhibition of MCP-1/CCR2 signaling offers protection against ethanol-induced damage to the developing CNS by reducing microglia activation. In this study, we used a third trimester equivalent mouse model as well as an immortalized microglia cell line (SIM-A9) of ethanol exposure to determine the role of MCP-1 and its receptor CCR2 in ethanol neurotoxicity in the developing brain. We found MCP-1 synthesis inhibitor Bindarit or CCR2 antagonist RS504393 decreased ethanol-induced apoptosis and microglial activation in the in the brain of postnatal 4 day-old mice. We also found that EtOH induces MCP-1 in SIM-A9 cells and blocking MCP-1/CCR2 signaling decreases Ethanol/MCP-1 induced SIM-A9 cell activation. In summary, our data suggest that inhibition of MCP-1/CCR2 signaling offers protection against ethanol-induced damage to the developing brain, the protection may be offered by reducing microglia activation.