Toll-like receptors play an important role in the innate immune response, although emerging evidence indicates their role in brain injury and neurodegeneration. Alcohol abuse induces brain damage and can sometimes lead to neurodegeneration. We recently found that ethanol can promote TLR4 signaling in glial cells by triggering the induction of inflammatory mediators and causing cell death, suggesting that the TLR4 response could be an important mechanism of ethanol-induced neuroinflammation. This study aims to establish the potential role of TLR4 in both ethanol-induced glial activation and brain damage. Here we report that TLR4 is critical for ethanol-induced inflammatory signaling in glial cells since the knockdown of TLR4, by using both small interfering RNA or cells from TLR4-deficient mice, abolished the activation of microtubule-associated protein kinase and nuclear factor-kappaB pathways and the production of inflammatory mediators by astrocytes. Our results demonstrate, for the first time, that whereas chronic ethanol intake upregulates the immunoreactive levels of CD11b (microglial marker) and glial fibrillary acidic protein (astrocyte marker), and also increases caspase-3 activity and inducible nitric oxide synthase, COX-2, and cytokine levels [interleukin (IL)-1beta, tumor necrosis factor-alpha, IL-6] in the cerebral cortex of female wild-type mice, TLR4 deficiency protects against ethanol-induced glial activation, induction of inflammatory mediators, and apoptosis. Our findings support the critical role of the TLR4 response in the neuroinflammation, brain injury, and possibly in the neurodegeneration induced by chronic ethanol intake [1].

1)

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