THE ETHANOL INDUCED-TLR4/NLRP3 INFLAMMATORY RESPONSE IN MICROGLIAL CELLS CAUSES BLOOD BRAIN BARRIER DYSFUNCTIONS

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We have previously reported that ethanol, by activating the innate immune receptors TLR4, triggers signalling inflammatory response, causing gliosis, neuroinflammation and brain damage. Ethanol can also activate other immune receptors, as NOD-like-receptors (NLRs), in particular the NLRP3-inflammasome in astroglial cells, stimulating the caspase-1 activation that allows the release of the mature interleukin-1β and interleukin-18 cytokines, mitochondria ROS generation and cell death by pyroptosis. However, whether microglia NLRs are also sensitive to the effects of ethanol contributing to the neuroinflammation is presently uncertain. Using cerebral cortex of chronic alcohol fed WT and TLR4−/−(TLR4-KO) mice, we show that chronic ethanol treatment enhances the TLR4 mediated-NLRP3 inflammasome complex activation and causes the up-regulation of pro-inflammatory cytokines (IL-33 and IFN-γ) and chemokines (CCL4, CXCL2 and CX3CL1). Studies in microglial cells in culture also indicate that ethanol induces NLRP3-inflammasome activation following the release of IL-1β and IL-18 cytokines. Likewise, we also observed that myeloperoxidase (MPO) activity of activated phagocytes, the CD45high/CD11b+ cell population, and the metalloproteinase-9 levels were up-regulated in the cortex of the ethanol-treated WT mice. Moreover, TLR4-supression eliminates most of these harmful ethanol effects described. Our results demonstrate that ethanol activates TLR4-mediated NLRP3-inflammasome complex in glial cells and suggest that stimulation of microglial cells could compromise the integrity and permeability of the blood brain barrier, events contributing to ethanol-induced neuroinflammation and brain damage. (Supported by RED-RTA: RD12-0028-007 and SAF2012-33747)