MOLECULAR MECHANISMS OF ETHANOL-INDUCED NEUROINFLAMMATION: ROLE OF GLIAL CELLS AND IL-1-RI/TLR4 RECEPTORS

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The brain is one of the major target organs of ethanol actions, and its chronic and acute alcohol intoxication lead to brain structure and function alterations, and in some cases to neurodegeneration. The neuropathological processes underlying these effects remain unclear. Glial cells and Toll-like receptors (TLRs) are vital players in CNS immune response and dysregulation of this response plays an important role in brain damage and neurodegeneration. We have previously demonstrated that ethanol promotes inflammatory processes in brain and glial cells by up-regulating cytokines and inflammatory mediators (iNOS, NO, COX-2), and by activating signalling pathways (IKK, MAPKs) and transcriptional factors (NF-kappaB, AP-1) implicated in inflammatory injury. TLR4/IL-1RI receptors are involved in the signaling inflammatory ethanol-induced response since blocking these receptors abolishes the production of ethanol-induced inflammatory mediators and cell death in astrocytes. We have proposed that ethanol-induced activation of IL-1RI/TLR4 is mediated by promoting receptors recruitment into the membrane microdomains *lipid rafts*, leading to receptor internalization and signalling. Our recent data demonstrate that stimulation of astrocytes with ethanol (10 mM), IL-1β or LPS, triggers the translocation of IL-1RI and/or TLR4 into *raft*/caveolae-enriched fractions, promoting the recruitment of signalling moleculesinto these microdomains. Pre-treatment with *lipid rafts* disrupting agents, such as nystatin or saponin, inhibits both the IL-1RI and TLR4 activation induced by ethanol, IL-1β or LPS. Immunofluorescence studies and confocal microscopy further revealed that either ethanol or IL-1? treatment triggers a rapid internalization of IL-1RI into enlarged cytoplasmic ring structures or caveosomes. In summary, our findings reveal a novel mechanism by which ethanol, by interacting with *lipid rafts* caveolae, promotes IL-1RI and TLR4 receptors recruitment, triggering their endocytosis via caveosomes and downstream signalling stimulation. These results suggest that TLRs receptors are important targets of ethanol-induced inflammatory damage in the brain. *Supported by Spanish Ministry of Science(SAF-2006—021789) and Inst.CarlosIII-RTA*
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