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AUTOPHAGY CONSTITUTES A PROTECTIVE MECHANISM AGAINST ETHANOL TOXICITY IN MOUSE GLIAL CELLS

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Ethanol induces brain damage and neurodegeneration by triggering inflammatory processes in glial cells through the activation of Toll-like receptor 4 (TLR4) signaling. Recent evidence indicates the role of protein degradation pathways in neurodegeneration and in alcoholic liver disease, but how these processes affect the brain remains elusive. We have recently demonstrated that chronic ethanol consumption alters proteolytic pathways in mouse brain, and that TLR4 participates in these proteolytic dysfunctions. We hereby aim to evaluate the effect of an acute dose of ethanol (50 mM) in the autophagy-lysosome pathway (ALP) on WT and TLR4-/- mouse glial cells, and how these changes affect cell death. Our results show that a single dose of ethanol induces an overexpression of several autophagy markers (ATG12, LC3-II and CTSB) and increases the number of autophagic vacuoles and lysosomes, along with the basification of the lysosomal pH. These changes could be caused by the reduction of the phosphorylation levels of the upstream autophagy inhibitor mTOR and the activation of the BECLIN-1 and ULK1 complexes. Interestingly, only minor changes were found between control and ethanol-treated TLR4-/- mouse glial cells. Furthermore, ethanol triggers the expression of inflammatory mediators such as iNOS and COX-2. The use of autophagy inhibitors aggravates this phenotype, both increasing inflammation and triggering cell death. Altogether, these results point towards a protective role of the ALP against ethanol toxicity in mouse glial cells in a TLR4-dependent manner. These findings could provide new insight into the mechanisms underlying ethanol-induced brain damage. (Supported by MEC, SAF2012-33747).