

Resumen en inglés

Alcohol is a neurotoxic compound and its abuse can cause brain damage and neurodegeneration. However, the neuropathological processes that produce these effects are not completely understood. Our group demonstrated for the first time that ethanol induces gliosis, neuroinflammation, brain damage and neurodegeneration by activating the brain innate immune system through the TLR4 receptor of glial cells. In addition, recent evidence suggests that alcohol alters the protein degradation processes in several pathologies such as alcoholic liver disease, but whether these proteolytic processes are also involved in ethanol-induced brain damage remains elusive. Therefore, we aim to evaluate the relationship between the two main proteolytic complexes, the ubiquitin-proteasome system and the autophagy-lysosome pathway, and the ethanol-induced brain damage, as well as the involvement of TLR4 receptors in these processes. To that end, we will use WT and TLR4^{-/-} mice chronically treated with ethanol in water for 5 months and we will compare them with their respective controls using techniques such as western blot, quantitative PCR, immunofluorescence, immunohistochemistry and cytometry. Similarly, we will also work with primary cultures of glial cells to evaluate the effect of an acute dose of alcohol *in vitro*. Our hypothesis is that by activating TLR4 signaling, ethanol causes neuroinflammation, oxidative stress and protein accumulation through a proteolytic systems dysfunction. This accumulation of protein aggregates may in turn stimulate the activation of the TLR4 receptor, amplifying the effects of ethanol in the production of brain damage and neurodegeneration.