Role of neuroinflammation in alcohol relapse: How does N-Acetylcysteine fit?

Fernández-Rodríguez, S[1]; Cano-Cebrián, MJ[1]; Esposito-Zapero C[1]; Guerri, C[2]; Granero, L; Polache, A[1] ; Zornoza, T[1] ;
[1]Department of Pharmacy and Pharmaceutical Technology and Parasitology, University of Valencia. Burjassot, 46100. Valencia, Spain
[2]Department of Cellular Pathology, Centro de Investigación Príncipe Felipe. Valencia, 46012. Valencia, Spain.

INTRODUCTION

Alcohol Use Disorder (AUD) is a chronic, progressive and recidivant disorder which supposes a serious health as well as economic problem worldwide. As reviewed by Erickson, it has been extensively described that alcohol consumption causes an increase of inflammatory mediators levels in the central nervous system (Erickson et al., 2019)

In the last years, **N-acetylcysteine** (NAC) has been proposed as a potential pharmacotherapy for the treatment of different substance use disorders. It has been demonstrated that NAC is able to reduce ethanol intake after a period of deprivation. Moreover this reduction is accompanied by a reduction of inflammatory signals in hippocampus during alcohol reintroduction (Israel et al., 2019). Other studies also shown that NAC reduces the inflammation caused by ethanol consumption in hippocampus and frontal cortex after cessation of oral gavage administration (Schneider et al., 2017).

OBJECTIVE

Our group have previously demonstrated that NAC is able to block the Alcohol Deprivation Effect (ADE) in long-term ethanol-experienced rats. In order to explore the mechanism underlying its anti-relapse efficacy, we have explored whether NAC is able to alter levels of **inflammatory mediators** in PFC during the **abstinence** period.

METHODS

Male Wistar rats were used in these experiments. Five groups were designed:

- **H2O** (n=6; rats exposed to water throughout 5 months)
- **Ethanol** (n=6; rats subjected to a long-term voluntary alcohol drinking procedure, using a four-bottle home cage paradigm (5%, 10%, 20% v/v ethanol solutions) during 5 months)
- Abstinence (n=15; rats subjected to a long-term voluntary alcohol drinking procedure, using a four-bottle home cage paradigm with several periods of ethanol exposure (6±2 weeks) and deprivation (2±1 weeks). In the fifth deprivation period they were subcutaneously treated with NAC 0 (**abstinence**) 60 (**NAC 60**) or 100 mg/kg (**NAC 100**) during 8 days once a day).

Prefrontal cortex, an area related to inhibitory control was dissected. RNA was extracted and quantitative PCR for IL-1β, IL-6, TNFα, HMGB1, iNOS and NFκB were carried out. When differences were detected, the Tukey post-hoc test was applied.

BIBLIOGRAPHY

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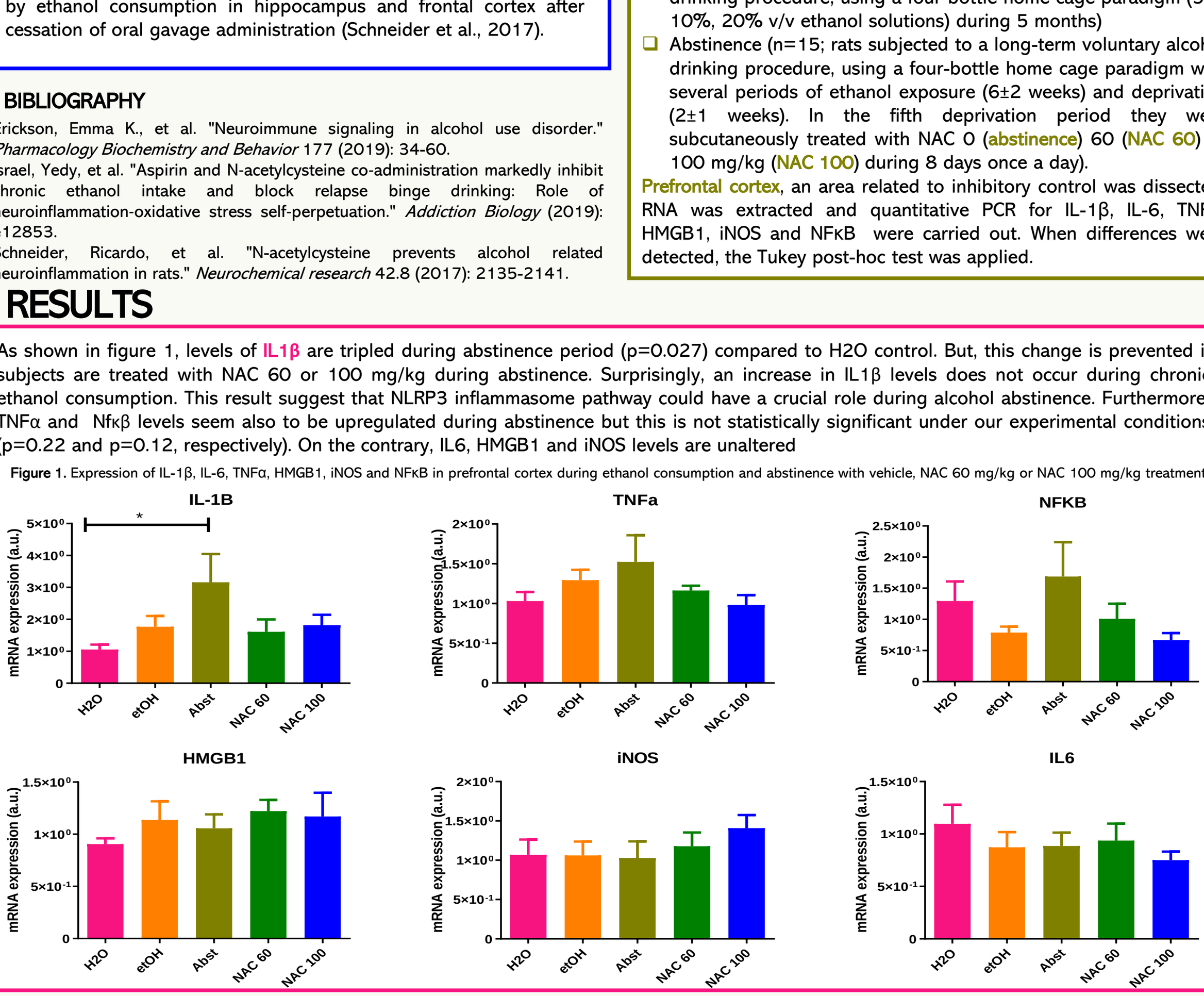
RESULTS

As shown in figure 1, levels of **IL1β** are tripled during abstinence period (p=0.027) compared to H2O control. But, this change is prevented if subjects are treated with NAC 60 or 100 mg/kg during abstinence. Surprisingly, an increase in IL1β levels does not occur during chronic ethanol consumption. This result suggest that NLRP3 inflammasome pathway could have a crucial role during alcohol abstinence. Furthermore, TNFα and Nfκβ levels seem also to be upregulated during abstinence but this is not statistically significant under our experimental conditions (p=0.22 and p=0.12, respectively). On the contrary, IL6, HMGB1 and iNOS levels are unaltered

Figure 1. Expression of IL-1β, IL-6, TNFα, HMGB1, iNOS and NFκB in prefrontal cortex during ethanol consumption and abstinence with vehicle, NAC 60 mg/kg or NAC 100 mg/kg treatment.



CONCLUSIONS

According to shown data, under our experimental conditions only IL1β levels are increased during abstinence period in prefrontal cortex. What is more interesting is that NAC treatment can avoid this upregulation. This effect could be responsable, at least in part, of the anti-relapse effects observed by our group. Further research is needed in order to clarify if NLP3-inflammosome pathway is involved in alcohol abstinence and relapse.

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https://www.uv.es/neuropharad/ **Contact:** sanfero5@uv.es