Untangling neural mechanisms regulating sex differences in alcohol use disorders (AUD)

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Poster

Neurobiología de enfermedades - Neurobiology of disease

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Excessive alcohol consumption poses a significant global health challenge, with profound social consequences. Previously, We have showed that alcohol intake results in aberrant prefrontal synaptic pruning and increased anxiety, mediated by NF-kB and microglial TNF production. Importantly, genetic or pharmacological blockade of TNF production, prevented such events. Here, by integrating behavioural, morphological, and proteomic analyses, we aims to provide a comprehensive, sex-specific perspective on the alcohol-induced neuroimmune and synaptic alterations.

Using a voluntary drinking model based on an intermittent ‘every-other-day’ (EOD) access paradigm, mice were given 15% (v/v) ethanol solution for a period of 4 weeks. Our data reveals distinct sex-dependent glial and synaptic adaptations to chronic alcohol exposure. Males exhibited increased astrocytic volume in the ventromedial PFC and hyper-ramification in the ventrolateral PFC, while females presented reduced astrocyte size and complexity. Microglia also showed sex-specific changes: males exhibited decreased microglial volume, whereas females displayed increased microglial size. Additionally, males showed increased anxiety and increased prefrontal

inhibitory synapse density, while females exhibited an increase in excitatory synapses and reduced anxiety-like behaviour. Importantly, proteomic data obtained from controls and alcohol exposed synaptosomes confirmed substantial sex- and alcohol-related differences, showing that in females alcohol seems to substantially affect fatty-acid metabolism and TCA cycle, impacting on glutamate and GABA function, while in males the most affected terms seem to be related with myelin and axon function.

Collectively, these results highlight the need to untangle the sex-specific mechanisms regulating the glia-neuron crosstalk in AUD.

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