



Proyecto PID2021-122795OB-I00 financiado por MCIN/AEI/10.13039/501100011033/ y por FEDER Una manera de hacer Europa

Identificación del proyecto:

ASTROcitos hipocampales: una conexión entre los Cannabinoides y la enfermedad de Alzheimer (ASTROCAD)

Descripción del proyecto:

The study of how glial cells, in particular astrocytes, participate in the development of neurodegenerative disorders such as AD disorders has become a hot topic in neuroscience. However, little is known regarding the mechanisms linking these astroglial dysfunctions and AD alterations. Our previous work indicates that CB1 receptors are functionally present in different neuronal types and in astrocytes, where they can control specific astroglial functions impacting complex mouse behavioral responses. Thus, a potential therapeutic target against AD are the specific CB1 receptors pools present in neurons and/or astrocytes although their specific involvement remains elusive. We have recently started a line of research in order to study these cell-type specific mechanisms using the APP/PS1 mice, a mouse model of AD. In this project, we want to focus on the potential involvement of astroglial functions in several behavioral phenotypes found in this mouse model.

Our recent findings suggest that cannabinoid treatment during an asymptomatic period could be a valid therapeutic strategy against behavioral alterations found in the APP/PS1 mice. In addition, using the APP/PS1 mice, we have revealed important sex-dependent behavioral phenotypes and sex-dependent changes on the astroglial expression of specific genes involved in bioenergetic and antioxidant processes. These results unveil the importance of sex and the cell-type specific analysis on (1) the understanding of the complex behavioral dysfunctions found in AD and, (2) how pharmacological interventions (e.g. cannabinoids) could exert their therapeutic value. However, we are far to fully understand which is the impact of sex and brain cell-types (i.e. astrocytes) on the cannabinoid-dependent effects in AD.

This proposal aims at investigating the role of astrocytes in the sex-dependent differences and the cannabinoid-induced behavioral effects found in the APP/PS1 mice. By using several genetic, genomic, behavioral, viral, pharmacological and imaging approaches, the ASTROCAD project will be divided by different specific aims in order to: perform a transcriptomic characterization of astrocytes in the APP/PS1 mice (Aim 1), use calcium imaging to couple astroglial activity and behavior in the APP/PS1 mice (Aim 2) and manipulate astroglial activity and/or specific mechanisms in the APP/PS1 mice (Aim 3). Thus, this project is highly relevant to better understand how astrocytes might be considered a potential cornerstone in AD research that could explain genotypic phenotypes, gender differences and the therapeutic effects of cannabinoid drugs. This is demonstrated in several ways: 1. It represents a thorough characterization in the APP/PS1 mice of sex-dependent astroglial mechanisms; 2. It will

decipher the astroglial molecular mechanisms underlying cannabinoid-induced improvements in this model; 3. It will bring important observations on how astroglial activity is coupled with behavioral manifestations; 4. By targeting hippocampal astrocytes, this project aims to provide a direct link between astrocytes and the behavioral phenotypes observed. In conclusion, I strongly believe that ASTROCAD, by exploring novel and promising scientific paths, will substantially contribute to advancing the comprehension of the mechanistic basis of AD.

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205.700,00€

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