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Efecto del síndrome metabólico provocado por una dieta rica en grasa en ratones APPswe/PS1dE9, modelo experimental de la enfermedad de Alzheimer, y posibles terapias farmacológicas

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CONCLUSIONES

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The conclusions of the present doctoral thesis are the following:

Effect of HFD in a presymptomatic stage of APP/PS1 familial AD mice model

1. The HFD favours the development of AD at 3-month-old of age through different mechanisms:
    a) The HFD increases APP and decreases BACE1 protein levels, resulting in an increase of $A\beta_{1-40}$ soluble and insoluble and βA_{1-42} insoluble in cortex and, therefore, an increase of plaque deposition. Moreover, the HFD decreases insulin degrading enzyme (IDE) protein levels, which also contributes to plaque deposition.
    b) The HFD together with Aβ shows a synergistic effect which favours cognitive loss.
    c) At the molecular level, the HFD provokes the decrease of p-CREB and PGC1α protein levels, suggesting that they could represent a potential risk factor in the onset and progression of AD. Therefore, their preservation in the brain might be a molecular target mechanism providing neuroprotection against metabolic AD.

Effect of chronic administration of DXI in APP/PS1 familial AD mice model

1. The chronic treatment of DXI provokes a reduction in the neuroinflammatory process, resulting in the decrease of NFT through c-ABL/CABLES/CDK5 pathway, reduction of Aβ deposition and enhancement of insulin signalling leading to a memory improvement.

2. This study demonstrates that chronic administration of DXI could exert multiples beneficial affects against AD development, as preventive treatment or as a coadjuvant drug together with others.

Effect of MEM in mixed preclinical mice model of obesity, induced by the intake of HFD, and familial AD

1. MEM ameliorates learning and memory deficits, activating insulin signalling pathway, decreasing PTP1B protein levels, inhibiting glial activation, as well as, enhancing synaptic proteins and decreasing Aβ deposition in obese APP/PS1 mice.

2. MEM improves peripheral parameters such as HFD-intake induced hyperglycaemia, insulin resistance and body weight gain in APP/PS1 but not in WT mice, suggesting that MEM could interact with Aβ in the brain, contributing synergically with HFD causing insulin resistance process in APP/PS1.

3. MEM ameliorates insulin signalling in the liver, regulating IRS2 and its downstream targets, suggesting that this drug could be a pontential treatment for T2DM and additional liver pathologies.