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P14. OBESITY-DRIVEN NEURODEGENERATIVE DISEASES: NEW INSIGHTS FOR NEW MOLECULAR INTERPLAYERS AND THERAPEUTIC TARGETS

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Neurodegenerative diseases are one of the main causes of worldwide disability and decreased quality of life. A link between neurodegeneration and obesity is opening novel research avenues in the search for therapeutic approaches. Unfortunately, current available treatments for both pathologies remain ineffective. Therefore, it is important to generate appropriate models to evaluate the relationship between obesity and neurodegeneration. The metabolic changes caused by obesity are able to modulate the central nervous system by altering the synaptic plasticity. In this study, we have investigated the changes in synaptic plasticity at areas implicated in cognitive function, such as the hippocampus and prefrontal Tau. GSK3β is a key enzyme responsible for the fine balance between the phosphorylated and not phosphorylated forms of Tau, modulating synaptic plasticity in these areas. Different endocannabinoid (ECs) system are able to interact and modify the activity of GSK3β. By molecular, biochemical and morphological studies, we found remarkable changes in the expression of phosphorylated tau form in hippocampus and prefrontal cortex of leptin knockout ob/ob mice which represent a model of obesity by mimicking the leptin inefficacy in the brain of mice made obese by a high fat diet. Furthermore, we found elevation of 2-AG and OX-A content in the hippocampus of ob/ob confirming that OX-A and 2-AG (2-arachidonoylglycerol) are able interplayers to increase or decrease, respectively, the phosphorylation of tau in opposite way. Unraveling the functional crosstalk between ECs and OX system in the regulation of Tau phosphorylation of in areas of the brain involved in cognitive function could reveal novel molecular players and pathways that might result in drug able targets.