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Molecular mechanisms linking obesity to neurodegeneration: focus on neuroinflammation

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Neuroinflammation and chronic activation of the innate immune response are associated with the early onset of neurodegenerative diseases. The finding that obesity and metabolic disorder are accompanied by chronic low-grade inflammation, astrogliosis, and the release of pro-inflammatory cytokines, has fundamentally changed our approach to the underlying early causes of neurodegenerative disturbances. This is of special relevance, since that from 2019 the World Health Organization recommends focusing on modifiable risk factors in the prevention of Alzheimer's Disease (AD). Diet composition is certainly one of these factors, especially by considering the massive worldwide consumption of a high-calorie diet, rich in fats and sugars (i.e. High Fat Diet – HFD - or Western diet), which induces multi-organ inflammation, including brain-blood barrier, adipose tissue, and gut-brain axis. In AD, synaptic loss and dysfunction are early and strongly correlated with cognitive impairment. Pre-fibrillar oligomeric beta-amyloid (Ab) and/or tau accumulate on synapses,and induce pathological synaptic dysfunction and loss. This communication provides an overview of our sequential studies linking obesity to neuroinflammation and neurodegeneration by exploiting *in vitro* and *in vivo* studies in a mouse model of HFD-induced obesity, also extended to the transgenic microglia CX3C-eGFP strain. Functional studies of synapses (patch-clamp recording, calcium imaging) have been extended by time-lapse cell imaging, confocal microscopy, CLEM and TEM, biochemical assays, LC-MS / MS, and NMR analysis of the mouse brain, and associated with tests for memory and cognitive performance. Data revealing the impact of leptin (a pro-inflammatory cytokine) and its interplay with the endocannabinoids and the neuropeptide Orexin-A (OX-A) in the regulation of neurogenesis and Tau phosphorylation will be discussed to provide new molecular insights to prevent neuroinflammation and neurodegeneration.

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