Dexibuprofen ameliorates peripheral and central risk factors associated with Alzheimer's disease in metabolically stressed APPswe/PS1dE9 mice

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Abstract

Background: Several studies stablished a relationship between metabolic disturbances and Alzheimer´s disease (AD) where inflammation plays a pivotal role. However, mechanisms involved still remain unclear. In the present study, we aimed to evaluate central and peripheral effects of dexibuprofen (DXI) in the progression of AD in APPswe/PS1dE9 (APP/PS1) female mice, a familial AD model, fed with high fat diet (HFD). Animals were fed either with conventional chow or with HFD, from their weaning until their sacrifice, at 6 months. Moreover, mice were divided into subgroups to which were administered drinking water or water supplemented with DXI (20 mg kg^{-1} d^{-1}) for 3 months. Before sacrifice, body weight, intraperitoneal glucose and insulin tolerance test (IP-ITT) were performed to evaluate peripheral parameters and also behavioral tests to determine cognitive decline. Moreover, molecular studies such as Western blot and RT-PCR were carried out in liver to confirm metabolic effects and in hippocampus to analyze several pathways considered hallmarks in AD. Results: Our studies demonstrate that DXI improved metabolic alterations observed in transgenic animals fed with HFD in vivo, data in accordance with those obtained at molecular level. Moreover, an improvement of cognitive decline and neuroinflammation among other alterations associated with AD were observed such as beta-amyloid plaque accumulation and unfolded protein response. Conclusions: Collectively, evidence suggest that chronic administration of DXI prevents the progression of AD through the regulation of inflammation which contribute to improve hallmarks of this pathology. Thus, this compound could constitute a novel therapeutic approach in the treatment of AD in a combined therapy.

Author keywords
Alzheimer´s disease; APPswe/PS1dE9; Cognitive deficits; Dexibuprofen; High fat diet; Metabolic alterations; neuroinflammation; Synapsis; Unfolded protein response; βA plaques