Dimethyl fumarate abridged tauo-/amyloidopathy in a D-Galactose/ ovariectomy-induced Alzheimer's-like disease: Modulation of AMPK/SIRT-1, AKT/CREB/BDNF, AKT/GSK-3ϐ, adiponectin/Adipo1R, and NF-əB/IL-1ϐ/ROS trajectories

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Abstract

Since the role of estrogen in postmenauposal-associated dementia is still debatable, this issue urges the search for other medications. Dimethyl fumarate (DMF) is a drug used for the treatment of multiple sclerosis and has shown a neuroprotective effect against other neurodegenerative diseases. Accordingly, the present study aimed to evaluate the effect of DMF on an experimental model of Alzheimer disease (AD) using D-galactose (D-Gal) administered to ovariectomized (OVX) rats, resembling a postmenopausal dementia paradigm. Adult 18-month old female Wistar rats were allocated into sham-operated and OVX/D-Gal groups that were either left untreated or treated with DMF for 56 days starting three weeks after sham-operation or ovariectomy. DMF succeeded to ameliorate cognitive (learning/short- and long-term memory) deficits and to enhance the dampened overall activity (NOR, Barnes-/Y-maze tests). These behavioral upturns were associated with increased intact neurons (Nissl stain) and a reduction in OVX/D-Gal-mediated hippocampal CA1 neurodegeneration and astrocyte activation assessed as GFAP immunoreactivity. Mechanistically, DMF suppressed the hippocampal contents of AD-surrogate markers; viz., apolipoprotein (APO)-E1, BACE1, Aϐ42, and hyperphosphorylated Tau. Additionally, DMF has augmented the neuroprotective parameters p-AKT, its downstream target CREB and BDNF. Besides, it activated AMPK, and enhanced SIRT-1, as well as antioxidant defenses (SOD, GSH). On the other hand, DMF inhibited the transcription factor NF-əB, IL-1ϐ, adiponectin/adiponectin receptor type (AdipoR)1, GSK-3ϐ, and MDA. Accordingly, in this postmenopausal AD model, DMF treatment by pursuing the adiponectin/AdipoR1, AMPK/SIRT-1, AKT/CREB/BDNF, AKT/GSK-3ϐ, and APO-E1 quartet hampered the associated tauo-/amyloidopathy and NF-əB-mediated oxidative/inflammatory responses to advance insights into its anti-amnesic effect.

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