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N, N-Dimethyltryptamine, a psychedelic, exerts nootropic effects by modulating mitochondria-associated endoplasmic reticulum membrane function in the models of Alzheimer's disease

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Abstract

Signaling between mitochondria-associated endoplasmic reticulum (ER) membranes (MAMs) regulates many neuronal functions, some of which are perturbed in Alzheimer's disease (AD). So the potential pharmacological intervention using mitochondria-ER modulators in AD models may be a promising therapeutic agent for AD. N, N-dimethyltryptamine (DMT), an agonist of the sigma-1 receptor (sig-1r), also belongs to one of the psychedelic compounds that may have nootropic effects. In this study, transgenic Alzheimer's disease model mice received intraperitoneal injection of 2 mg/kg DMT for 3 weeks and were tested in the Morris water maze (MWM) test and novel objective recognition (NOR) test. The model mice showed a striking decrease in time spent in the target quadrant and the familiar objects. DMT reversed the two behavioral variables. DMT also effectively abolished hippocampal Aβ deposits and ameliorated synaptic impairment in the hippocampus. The model mice also exhibited elevated expression of MAM proteins. DMT modulation the expression of these proteins. In vitro studies showed that DMT promoted neuronal cell viability and had strong neuroprotective effects on the primary hippocampal cells. DMT promoted calcium influx to mitochondria from ER, thereby increasing the tricarboxylic acid (TCA) cycle in the mitochondria and increasing ATP production.

Additionally, DMT protected against mitochondrial structure and functions in the hippocampus, including improved mitochondrial membrane potential (MMP) and enhanced mitochondrial oxidative phosphorylation (OXPHOS) capacity. The experimental evidence in this study indicated that sig-1r activation might contribute to the potent anti-AD effects of DMT. Overall, our results suggest DMT is a promising preventive or therapeutic agent for AD.

Keywords: Alzheimer's disease, cognitive impairment, endoplasmic reticulum, mitochondrial dysfunction; N, N-Dimethyltryptamine