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Small Molecule Inhibits Metal-Dependent and -Independent Multifaceted Toxicity of Alzheimer's Disease

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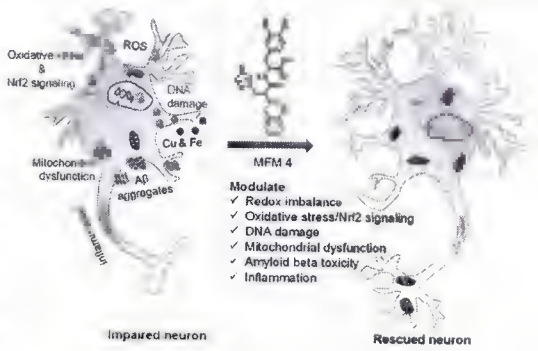
Supporting Information

ABSTRACT: Alzheimer's disease (AD) is one of the most devastating forms of dementia, without reliable treatments to cure, delay the onset, or prevent the disease progression. The proposed toxic mechanisms of AD include amyloidogenesis of amyloid β (Aβ), metal ion dyshomeostasis, redox active metal−Aβ inclusion complex formation, and generation of excessive reactive oxygen and nitrogen species (ROS and RNS). The imbalance in redox homeostasis causes oxidative stress, DNA damage, mitochondrial dysfunction, and inflammation, which collectively become a major hurdle in the development of effective therapeutic agents for multifactorial AD. This necessitates a multifunctional strategy to develop effective therapeutic agents to inhibit multifaceted toxicity. In this context, we report a rational design, synthesis, and detailed study to identify a small molecule multifunctional modulator (MFM) inspired by the human origin tripeptide. The lead, MFM 4, chelates and sequesters metal ions, disrupts their redox cycles, prevents excessive ROS production and oxidative stress, ameliorates oxidative DNA damage and mitochondrial dysfunction, and modulates Nrf2 protein signaling under oxidative stress conditions by eliminating the toxic stress elements. The MFM 4 was found to inhibit metal-dependent and -independent Aβ aggregation and qualified as a suitable candidate to inhibit Aβ-induced neuronal toxicity. The NMR spectroscopy study revealed molecular-level interactions of 4 with Aβ42, which explain the mechanism of aggregation inhibition. Furthermore, 4 effectively inhibited inflammation as revealed by reduction in nitric oxide (NO) production in LPS-activated glial cells. These key features make 4 a potential MFM platform to develop therapeutic agents for metal (Cu, Zn and Fe)-dependent and -independent multifaceted Aβ toxicity of AD.



KEYWORDS: *amyloid toxicity, mitochondrial dysfunction, oxidative stress, Nrf2 signaling, inflammation, multifunctional modulator*

INTRODUCTION

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders accounting for 70−80% of all forms of dementia.[1] The disease symptoms include cognitive decline, memory loss, and behavioral disability, all of which ultimately lead to death.[2,3] This devastating ailment has reached epidemic proportions worldwide owing to the lack of effective drugs.[4] Although the precise etiology of the disease is poorly understood, production, aggregation, and deposition of Aβ peptides in the brain as senile plaques is strongly implicated in AD progression.[5−7] This Aβ42 is highly amyloidogenic and exhibits high propensity to undergo aggregation through hydrophobic interactions and ordered β-sheet formation to form polymorphic soluble oligomers, protofibrils, and insoluble fibrillar aggregates.[5,7−10] The Aβ toxicity is aggravated in the presence of metal ions such as copper and iron owing to the formation of Aβ−metal complexes, which accelerate the process of aggregation to generate highly toxic polymorphic Aβ−metal species.[11,12] These polymorphic Aβ species are implicated in membrane toxicity and mitochondrial dysfunction and trigger various neurotoxic cascade processes.[9,13] Furthermore, the inclusion of redox-active metal ions (Cu^{II} and Fe^{III}) in Aβ species triggers Fenton-type reaction in the reducing environment to generate reactive oxygen and nitrogen species (ROS and RNS, respectively), which induce neuronal oxidative stress.[5,9,14] The generation of excessive ROS damages DNA, which contributes to additional toxicity and neuronal death.[7,11,14] The failure of cellular redox homeostasis (oxidative stress) is governed by Nrf2 signaling, a nuclear transcription factor, which adjusts redox homeostasis by activating an array of antioxidant genes.[15] Further, polymorphic Aβ species activate neuroglia cells via the toll-like-receptor 4 (TLR4) signaling pathway, leading to neuro-inflammation.[16,17] Therefore, neuronal impairment through oxidative stress, inflammation, and mitochondrial dysfunction are the manifestations of multifaceted toxicity induced by Aβ−metal aggregation species in the AD brain.[5,18,19] This emphasizes the need for a novel drug design strategy to

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