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Curcumin can influence synaptic dysfunction in APPswe/PS1dE9 mice

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Abstract *Objective:* Synaptic loss in the hippocampus in Alzheimer's disease (AD) has been shown to be closely associated with the cognitive impairment. Synaptic dysfunction is a pathological feature that occurs prior to synaptic loss and mainly depends on structural changes and alterations of synaptic proteins. Evidence has suggested that curcumin, obtained from the traditional Chinese medicine—Turmeric (*Curcuma longa L.*), can ameliorate cognitive impairment, but few studies have focused on the mechanism by which curcumin affects synapses at early stages of AD. Therefore, we performed a study to investigate whether curcumin exerted its effect on synapses at the early stage in AD.
Methods: We used 3-month-old APPswe/PS1dE9 mice and wild type (WT) littermates of the APPswe/PS1dE9 mice from the same colony as the normal controls. Seventy-five APPswe/PS1dE9 mice were allocated to the Model group, Rosiglitazone group, and Curcumin groups randomly. The Wild and Model groups were orally administered an equal amount of 0.5% carboxymethyl cellulose (CMC). We observed the ultrastructure of synapses in the CA1 area of hippocampus and analyzed the expression levels of PSD95 and Shank1, two important synapse-associated proteins, in APPswe/PS1dE9 mice by immunohistochemical staining and western blot after gavage for three months.

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Results: Our findings showed that curcumin treatment not only improved the quantity and ultrastructure of synapses but also increased the expression of PSD95 and Shank1.
Conclusion: The results indicate that curcumin improves synaptic dysfunction and the potential mechanism may involve improving the structure of synapses and regulating the synapse related proteins PSD95 and Shank1.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder clinically characterized by cognitive and memorial dysfunction, even personality changes.[1] According to the 2016 World Alzheimer Report, 47 million people suffer from dementia in the world. It is estimated that the number of patients with dementia will reach more than 131 million by 2050. Dementia has a major economic impact on the global society. US$ 818 billion will be spent on it, and dementia will be a trillion-dollar disease by 2018.[2]

The main neuropathological changes in AD include neuronal and synaptic loss, neurofibrillary tangles, and abnormal accumulation of β-amyloid (Aβ).[1,3] Significant loss of synapses in the hippocampus has been observed in AD.[4] Synaptic dysfunction is an early pathological feature that occurs prior to synaptic loss, neurodegeneration, and memory disorders. It mainly depends on structural changes and alterations of synaptic proteins, along with shrinkage or enlargement of dendritic spines and the postsynaptic density (PSD).[5] Synaptic proteins, such as PSD95 and synaptophysin, have been shown to change in the brain in AD patients.[6] Shank plays a significant role in the maintenance of synaptic structures and the postsynaptic platform.[7] It was demonstrated that Shank1 and synapse density were significantly decreased in the AD hippocampal neurons.[6,8]

To date, no effective treatments have been developed for AD.[4] There is a pressing need to develop effective drugs that can delay or prevent the progression of AD. Several researches have shown that some active compounds from plants exert neuroprotective effect against neurodegenerative diseases, including AD.[9] Curcumin is a polyphenolic antioxidant obtained from Turmeric (*Curcuma longa L.*).[10] Some studies have illustrated multiple effects of curcumin, including antioxidant, anti-inflammatory, and anti-cancer activities.[11,12] Curcumin has recently been adopted for the prevention and cure of AD, and its neuroprotective effect in AD has been intensively investigated.[13–15] However, the results of these researches are controversial.[16,17] It may be partly owing to the very bad solubility and absorption of curcumin.[18] Some researchers have demonstrated that curcumin can penetrate the blood brain barrier (BBB) and will concentrate chiefly in the hippocampus to have a therapeutic effect even at a low concentration.[19,20]

APPswe/PS1dE9 double transgenic mice show increases in Aβ42 and Aβ-derived diffusible ligands (ADDLs) and therefore can serve as a model for the pathological changes in AD.[21,22] It has been reported that curcumin treatment attenuated cognitive impairment in APPswe/PS1dE9 double transgenic mice.[13,15] We also have demonstrated that curcumin reduced Aβ-induced toxicity and the aggregation of Aβ into fibrils, possibly through inhibiting presenilin2 and/or increasing degrading enzymes.[13] Synaptic dysfunction and loss are closely related to cognitive impairment[23] which can be induced by Aβ[24]; however, few studies have focused on the mechanism by which curcumin affects synapses at the early stage of AD. Therefore, we designed a series of experiments to investigate the protective effect of curcumin on synapses. Our previous study has demonstrated that curcumin can improve the structure and quantity of synapses in nine-month-old APPswe/PS1dE9 double transgenic mice.[25] Synaptic dysfunction is an early pathological feature in AD progression,[5] so we performed a further research to investigate whether and the possible mechanism by which curcumin exerts its effect on synapses in the early stages of AD, by observing the ultrastructure of synapses in the CA1 area of the hippocampus and the expression of the synaptic proteins PSD95 and Shank1 in six-month-old APPswe/PS1dE9 mice after short-term treatment.

Materials and methods

Tested drug and preparation

Curcumin (Cat. No. C1386) was provided by Sigma—Aldrich (St. Louis, MO), and Rosiglitazone maleate (RSG) (Cat. No. 09060108) was obtained from GlaxoSmithKline Ltd. Co. (Tianjin, China). Curcumin and RSG were dissolved in 0.5% sodium carboxymethyl cellulose (CMC).

Animals

APPswe/PS1dE9 mice and wild type (WT) C57/BL6J littermates of the APPswe/PS1dE9 mice (three months old, 25 ± 3 g) were provided by the Institute of Laboratory Animal Science, Chinese Academy of Medical Sciences [SCXK (Beijing) 2009-0004]. Both kinds of mice were raised at 22 ± 2°C with 55% ± 5% humidity in the Barrier Environment Animal Lab of Dongzhimen Hospital, affiliated with Beijing University of Chinese Medicine (BUCM) [SYXK (Beijing) 2009-0028].

Ethical approval

Animal experiments conformed to published guidelines (NIH Guide for the Care and Use of Laboratory Animals) and were

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