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BRAIN RESEARCH

Research Report

Curcumin protects against glutamate excitotoxicity in rat cerebral cortical neurons by increasing brain-derived neurotrophic factor level and activating TrkB

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ABSTRACT

Curcumin is a major active component isolated from *Curcuma longa*. Previously, we have reported its significant antidepressant effect. However, the mechanisms underlying the antidepressant effects are still obscure. In the present study, we explored the effect of curcumin against glutamate excitotoxicity, mainly focusing on the neuroprotective effects of curcumin on the expression of Brain-Derived Neurotrophic Factor (BDNF), which is deeply involved in the etiology and treatment of depression. Exposure of rat cortical neurons to 10 μM glutamate for 24 h caused a significant decrease in BDNF level, accompanied with reduced cell viability and enhanced cell apoptosis. Pretreatment of neurons with curcumin reversed the BDNF expression and cell viability in a dose- and time-dependent manner. However, K252a, a Trk receptor inhibitor which is known to inhibit the activity of BDNF, could block the survival-promoting effect of curcumin. In addition, the up-regulation of BDNF levels by curcumin was also suppressed by K252a. Taken together, these results suggest that the neuroprotective effect of curcumin might be mediated via BDNF/TrkB signaling pathway.

1. Introduction

As a severe clinical problem across the globe, major depression has been ranked among the most burdensome diseases to society by the World Health Organization (McKenna et al., 2005). Despite the increased prevalence of depression, relatively few prospective agents with high efficacy have been reported, and most of the currently available antidepressants are often associated with several undesirable side effects (Nemeroff, 2007). Thus, identification of powerful and safe therapeutic tools is still in significant need. Since a growing number of herbal medicines have been found to be effective in the treatment of psychiatric diseases (Kessler et al., 2001), such as the St. John's wort (Linde and Knüppel, 2005), traditional herbs may become a novel pharmacotherapy in the treatment of depression.

Curcuma longa has been found to be effective in treating neuropsychiatric disorders since ancient time in China (Kong et al., 2001). As the major component of *C. longa*, curcumin has also been discovered to have a variety of pharmacological activities, including anti-inflammatory, antioxidant, anti-proliferative, and neuroprotective effects (Motterlini et al., 2000; Mehta et al., 1997; Thiyagarajan and Sharma, 2004). Recently, several lines of investigations have shown that

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in cultured neurons and neurally related cells, curcumin protects against apoptosis induced by a variety of insults, including N-methyl-D-aspartate (NMDA) treatment (Matteucci et al., 2005), 1-methyl-4-phenylpridinium ion (MPP^+) administration (Chen et al., 2006) and H_2O_2 exposure (Vajragupta et al., 2003). Previously, we demonstrated that acute treatment of curcumin dramatically reduced the immobility time in the forced swimming test and tail suspension test in mice (Xu et al., 2005). Moreover, chronic curcumin administration was able to modulate the dysfunction of HPA axis in stressed rats (Xu et al., 2006). However, the molecular and cellular mechanisms by which curcumin exerts its antidepressant-like effects are still unknown.

Accumulating evidence suggests that neurotrophins play a crucial role in the survival of mammalian nervous system. As an important member of the neurotrophic family, Brain-Derived Neurotrophic Factor (BDNF) promotes neuronal survival, differentiation and morphology (Einat and Manji, 2006). Decreased BDNF activity results in aggravated death of hippocampal neurons after global forebrain ischemia (Larsson et al., 1999).The essential role of BDNF in the normal development of the brain is further confirmed by the neuronal phenotypic abnormalities in BDNF knockout mice (Ernfors et al., 1994; Jones et al., 1994; Marty et al., 1996). Recently, the involvement of BDNF and its receptor TrkB in mood disorders and antidepressant effects has been intensively investigated (Castren et al., 2006; Dias et al., 2003). The antidepressant treatment is able to attenuate the reduced levels of BDNF found in brain and blood samples of depressed patients (Chen et al., 2001; Karege et al., 2005; Shimizu et al., 2003). Furthermore, transgenic mice with reduced BDNF-mediated signaling in brain are insensitive to some antidepressants in the behavioral tests (Sairanen et al., 2005). Increasing evidence supports the notion that BDNF release and signaling are sufficient and necessary for the neuroprotective effect of antidepressants.

Since BDNF is necessary in the action of various kinds of antidepressants, we explored whether BDNF and TrkB activation is involved in the neuroprotective effect of curcumin in the present study. In the present study, we focused our studies on the cultured rat cerebral cortical neurons exposed to glutamate-induced lesion which has been suggested in the pathogenesis of many neurodegenerative diseases.

2. Results

2.1. *Curcumin protects cortical neurons against glutamate excitotoxicity*

Cortical neurons were exposed to glutamate (10 μM) for 24 h with or without curcumin pretreatment. In the dose-dependent study, neurons were pretreated with 0.625, 1.25, 2.5, 5, 10, 20, 40 μM curcumin for 24 h. In the time-dependent study, cells were pretreated with 10 μM curcumin for 1, 3, 6, 12, 18, 24, 48 h.

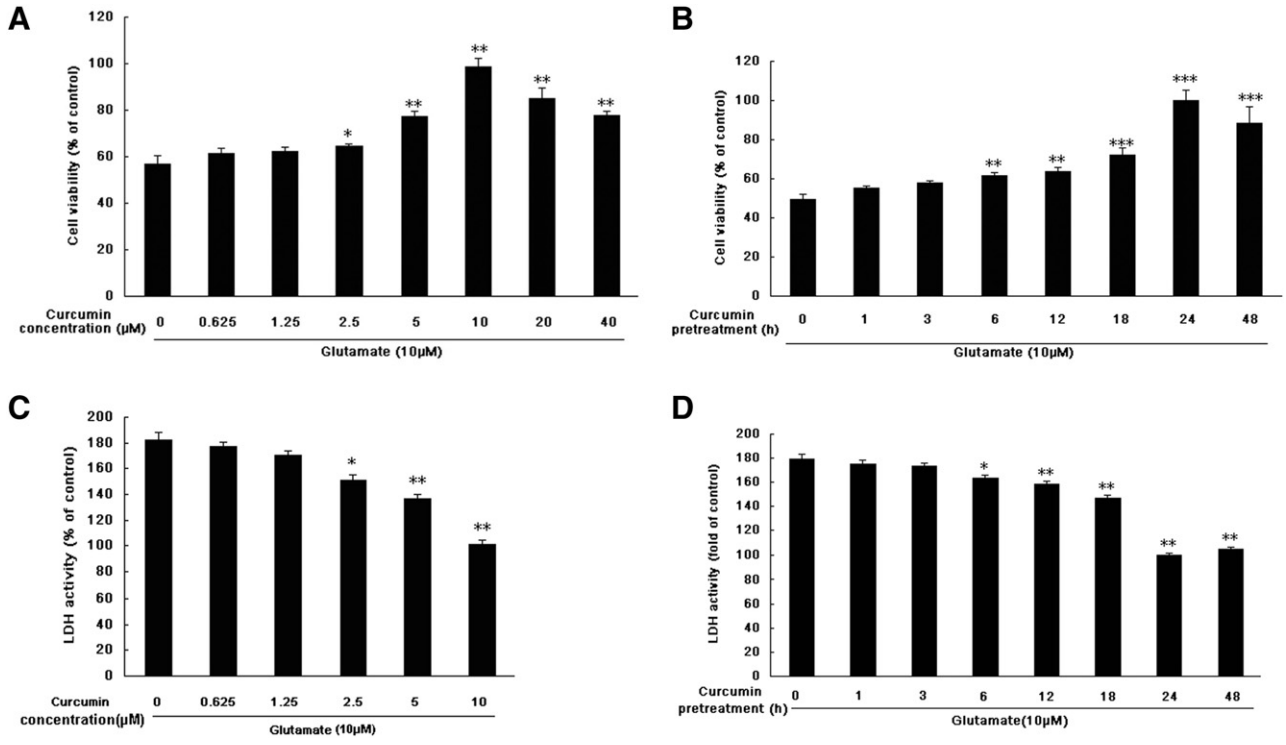

Fig. 1 – Neuroprotection of curcumin against glutamate excitotoxicity in cultures of cortical neurons. The neuroprotective effect of curcumin (10 μM, 24 h) was analyzed by MTT assay (A–B) and measuring lactate dehydrogenase (LDH) activities in the supernatant culture medium (C–D). Curcumin protected the neurons against glutamate (10 μM, 24 h)-induced decrease in cell viability dose- and time-dependently ($^*p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, versus glutamate-treated, injured groups). The data shown here are the mean ± S.E.M. of six separate experiments.