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BRAIN RESEARCH

Research Report

Curcumin reverses the effects of chronic stress on behavior, the HPA axis, BDNF expression and phosphorylation of CREB

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ABSTRACT

Curcuma longa is a major constituent of the traditional Chinese medicine Xiaoyao-san, which has been used to effectively manage stress and depression-related disorders in China. Curcumin is the active component of curcuma longa, and its antidepressant effects were described in our prior studies in mouse models of behavioral despair. We hypothesized that curcumin may also alleviate stress-induced depressive-like behaviors and hypothalamic–pituitary–adrenal (HPA) axis dysfunction. Thus in present study we assessed whether curcumin treatment (2.5, 5 and 10 mg/kg, p.o.) affects behavior in a chronic unpredictable stress model of depression in rats and examined what its molecular targets may be. We found that subjecting animals to the chronic stress protocol for 20 days resulted in performance deficits in the shuttle-box task and several physiological effects, such as an abnormal adrenal gland weight to body weight (AG/B) ratio and increased thickness of the adrenal cortex as well as elevated serum corticosterone levels and reduced glucocorticoid receptor (GR) mRNA expression. These changes were reversed by chronic curcumin administration (5 or 10 mg/kg, p.o.). In addition, we also found that the chronic stress procedure induced a down-regulation of brain-derived neurotrophic factor (BDNF) protein levels and reduced the ratio of phosphorylated cAMP response element-binding protein (pCREB) to CREB levels (pCREB/CREB) in the hippocampus and frontal cortex of stressed rats. Furthermore, these stress-induced decreases in BDNF and pCREB/CREB were also blocked by chronic curcumin administration (5 or 10 mg/kg, p.o.). These results provide compelling evidence that the behavioral effects of curcumin in chronically stressed animals, and by extension humans, may be related to their modulating effects on the HPA axis and neurotrophin factor expressions.

1. Introduction

At present, there are three main kinds of classical antidepressants in clinical practice, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). Most of these drugs, however, have undesirable side effects and their mechanisms of action have not been satisfactorily resolved. Therefore, seeking safe and effective antidepressant agents from traditional herbs may enable scientists to uncover novel treatments for depressive disorders and may further reveal as yet unknown mechanisms by which depressive symptoms can be alleviated.

Curcuma longa is commonly found in traditional Chinese herbal medicines, such as Jieyu-wan and Xiaoyao-san, which

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are used to treat the symptoms of mental stress, hypochondriac pain and mania. As the major active component of curcuma longa, curcumin has been reported to have antioxidant, anti-inflammatory, immuno-modulatory and neuroprotective activities (Motterlini et al., 2000; Thiyagarajan and Sharma, 2004). Previous studies in our laboratory showed that acute curcumin administration significantly decreased immobility time in the tail suspension and forced swim tests in mice (Xu et al., 2005b). We also demonstrated that chronic curcumin administration has an antidepressant effect in the olfactory bulbectomy model of depression in rats, which suggests that the central monoaminergic neurotransmitter systems may be involved in the anti-depressive effects of curcumin (Xu et al., 2005c). However, studies investigating the molecular targets of curcumin relevant to its antidepressant effects have not been done.

A large number of clinical observations have suggested that stress can act as a precipitating factor in the onset of affective illnesses, especially major depression (Bidzinska, 1984). The pathophysiology of depression and the neurobiology of stress are linked by their shared association with the hypothalamic–pituitary–adrenal (HPA) axis and in particular by their shared association with serotonin and norepinephrine containing neuronal systems (Breslow et al., 1989). In animals, several studies have demonstrated that the behavioral deficits and the abnormalities in the neuroendocrine system that are induced by exposure to uncontrollable and unpredictable chronic stress, such as hypoactivity in the open field and aberrations in the HPA system, can be reversed by antidepressant treatments (Kennett et al., 1986; Murua et al., 1991; Reul et al., 1993; Mizoguchi et al., 2002; Soblosky, 1986). These studies also revealed that rats exposed to a chronic unpredictable stress paradigm exhibited attenuated HPA axis feedback and abnormal gene expression. Indeed stress-associated behavioral changes were observed together with elevated corticosterone levels and decreased glucocorticoid receptor (GR) levels in the hippocampus and some other brain regions (Holsboer, 1999).

To our knowledge, studies examining the relationship between the neuroendocrine effects of chronic stress and those of curcumin treatment are lacking. Therefore, in the present study, we used an unpredictable chronic stress paradigm to determine whether chronic curcumin treatment can alleviate stress-induced behavioral abnormalities and corresponding gene changes in the HPA axis. In addition, to further investigate the possible molecular mechanisms that may be mediating the therapeutic effects of curcumin, we assessed the expression levels of brain-derived neurotrophic factor (BDNF) protein and the portion of its upstream target cAMP response element-binding protein (CREB) that is activated (phosphorylated CREB (pCREB)) in the hippocampus and frontal cortex.

2. Results

2.1. *The effects of curcumin on the number of escape failures in the shuttle box task*

As shown in Fig. 1, chronically stressed rats exhibited escape response deficits. Over the testing period, which included 30 footshock trials, the control rats on average failed to escape only twice. Meanwhile, the stressed rats subjected to the same paradigm failed to escape an average of ten times ($F(5,37)=3.13$, $p<0.01$ vs. non-stressed controls). Chronic curcumin (10 mg/kg, p.o.) administration significantly reduced the number of escape failures in stressed rats ($F(5,37)=3.13$, $p<0.05$ vs. vehicle-treated, stressed rats). A similar reduction of failures was found in stressed rats treated with the tricyclic antidepressant imipramine (10 mg/kg, i.p.; $F(5,37)=3.13$, $p<0.05$ vs. vehicle-treated, stressed rats). No differences were observed when administered with 10 mg/kg curcumin or imipramine as compared with non-stressed controls.

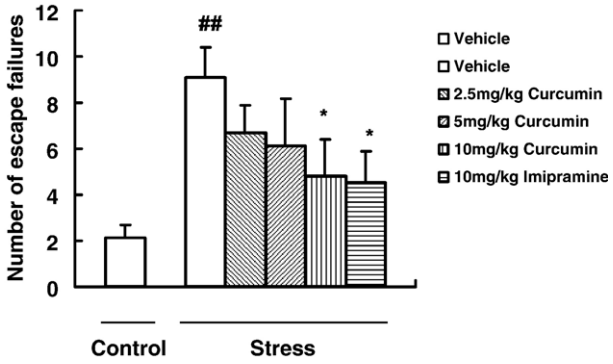

Fig. 1 – The effects of curcumin on shuttle-box behavior in stressed rats. Rats were administered vehicle, curcumin (2.5, 5 and 10 mg/kg, p.o.) or imipramine (10 mg/kg, i.p.) and the mean number of escape failures over 30 trials was quantified. Mean values ± SEM are shown ($n=8$–9 rats per group). $^{\#\#}p<0.01$ vs. Non-stressed control group. $^{*}p<0.05$ vs. vehicle-treated, stressed group.

2.2. *The effects of curcumin on body weight, the ratio of adrenal gland weight to body weight and thickness of adrenal cortex*

The effects of chronic stress and the administration of curcumin on body weight, the ratio of adrenal gland weight to body weight (AG/B) and the thickness of adrenal cortex are summarized in Table 1. No difference in the initial body weight was observed in any experimental group. Chronic stress significantly decreased body weight ($F(5,30)=12.69$, $p<0.05$), and significantly increased both the AG/B ($F(5,30)=6.69$, $p<0.05$) and the thickness of adrenal cortex ($F(5,30)=23.11$, $p<0.01$) relative to the non-stressed control rats. The chronic stress-induced decrease in body weight was not significantly affected by the 2.5, 5 or 10 mg/kg curcumin treatment; however, the increases in the AG/B and the thickness of adrenal cortex were ameliorated by the drug treatment ($F(5,30)=6.69$, $p<0.01$; $F(5,30)=23.11$, $p<0.001$). The positive control treatment with imipramine (10 mg/kg, i.p.) had similar effects on the AG/B and the thickness of the adrenal cortex ($F(5,30)=6.69$, $p<0.001$; $F(5,30)=23.11$, $p<0.001$,).

2.3. *The effects of curcumin on serum corticosterone levels*

The chronic stress paradigm caused a significant elevation of basal serum corticosterone levels relative to the non-stressed