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The effects of curcumin on depressive-like behaviors in mice

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Abstract

Curcuma longa is a major constituent of Xiaoyao-san, the traditional Chinese medicinal formula, which has been used effectively to treat depression-related diseases in China. There is no information available about the antidepressant activity of curcumin, the active component of curcuma longa. In the present study, we analyzed the effects of curcumin on depressive-like behaviors in mice, using two animal models of depression. Our results showed that curcumin treatment at 5 and 10 mg/kg (p.o.) significantly reduced the duration of immobility in both the tail suspension and forced swimming tests. These doses that affected the immobile response did not affect locomotor activity. In addition, the neurochemical assays showed that curcumin produced a marked increase of serotonin and noradrenaline levels at 10 mg/kg in both the frontal cortex and hippocampus. Dopamine levels were also increased in the frontal cortex and the striatum. Moreover, curcumin was found to inhibit monoamine oxidase activity in the mouse brain. These findings suggest that the antidepressant-like effects of curcumin may involve the central monoaminergic neurotransmitter systems.

Keywords: Curcumin; Forced swimming; Tail suspension; Locomotor activity; Antidepressant-like effect; Monoamine; Monoamine oxidase; Mice

1. Introduction

Several traditional Chinese herbal medicines, such as Xiaoyao-san and Jieyu-wan, prescribed a thousand years ago by the famous Chinese folk doctor Zhong-jing Zhang, have been used in the treatment of mental stress, hypochondriac distensive pain, hysteria and manic-depressive illness. Various findings in recent preclinical studies have supported the therapeutic value of herbal medicines in a clinical setting (Fan, 1996; Zhao, 2003). In laboratory studies of animals, Xiaoyao-san has also been shown to have antidepressive-like effects using the tail suspension and forced swimming tests (Wang et al., 2002; Xu et al., 2003).

Curcuma longa (turmeric) is commonly found in traditional Chinese herbal medicines, including Xiaoyao-san and Jieyu-wan, and has been shown to have antidepressant effects in mouse models of behavioral despair tests (Yu et al., 2002). In contrast, no information is available about the antidepressant activity of curcumin, which is a major active component of curcuma longa. Curcumin has been widely used as an antioxidant, anti-inflammatory, immunomodulatory and cancer chemopreventive agent for hundreds of years (Roberto et al., 2000; Yoshiyuki et al., 2003; Clarissa et al., 2003; Mazumder et al., 1995). In addition, curcumin has been shown to be efficacious in preclinical models of neurodegenerative diseases (Frautschy et al., 2001; Rajakrishnan et al., 1999). Furthermore, some dietary-derived food constituents, including curcumin, attenuate the activity the monoamine oxidase enzyme in C6 glial cells. Monoamine oxidase causes oxidative deamination of biogenic amines and xenobiotics, and regulates the intracellular concentration of catecholamines and 5-HT in the brain. Therefore, the abnormal function of this enzyme is thought to be involved in several psychiatric and age-related neurological disorders, such as depression and Parkinson's disease (Mazzio et al., 1998).

In view of the above observations, we wondered if curcumin would exert antidepressant-like activities in behavioral despair tests. Evidence suggests that drugs that are effective antidepressants increase the availability of monoamines such as serotonin, noradrenaline and dopamine.

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This happens either by preventing enzymatic breakdown, as in the case of monoamine oxidase inhibitors, or by preventing monoamine reuptake, as in the case of the tricyclic antidepressants. In this study, we assessed the potential antidepressant-like effects of curcumin by means of behavioral, pharmacological and neurochemical procedures.

2. Materials and methods

2.1. Animals

Male ICR mice (20–25 g) were obtained from the Department of Laboratory Animal Science, Peking University Health Science Center (Beijing, China). On arrival, the animals were housed ten per cage and acclimatized to a colony room with controlled ambient temperature (22±1 °C), humidity (50±10%) and a 12 h light/dark cycle. They were fed with standard diet and water ad libitum and were allowed to acclimate 7 days before they were used. In the case of oral drug administration, animals were fasted for 12 h before they were tested. The experiments were performed between 10:00 and 15:00 h. All experiments were conducted in accordance with the European Community guidelines for the use of experimental animals and approved by the Peking University Committee on Animal Care and Use.

2.2. Drugs and drug administration

Curcumin, imipramine hydrochloride, kynuramine dihydrobromide, 4-hydroxyquinoline, clorgyline, deprenyl, 5-hydroxytryptamine (5-HT), noradrenaline, dopamine, 5-hydroxyindoleacetic acid (5-HIAA) and 4-dihydroxyphenylacetic acid (DOPAC) were purchased from Sigma Chemical Co., (USA). Moclobemide hydrochloride was provided by the Beijing Institute of Pharmacology and Toxicology (China). For oral administration, curcumin was dissolved in peanut oil and diluted to the desired concentration on the day of testing and moclobemide was dissolved in redistilled water. For intraperitoneal injection, imipramine was dissolved in redistilled water. In this study, various doses of curcumin (1.25, 2.5, 5, 10 mg/kg) and moclobemide (20 mg/kg) were administered (p.o.) 60 min and imipramine (10 mg/kg) was injected (i.p.) 30 min before the test.

2.3. Tail suspension test

The tail suspension test was based on the method of Steru (Steru et al., 1985). Animals were suspended 50 cm above the floor by means of an adhesive tape, placed approximately 1 cm from the tip of the tail. The time during which mice remained immobile was quantified during a test period of 6 min. Mice were considered immobile only when they hung passively and completely motionless.

2.4. Forced swimming test

The forced swimming test employed was similar to that described elsewhere (Porsolt et al., 1977, 1978). Briefly, mice had a swimming-stress session for 15 min (pre-test), 24 h before being individually placed in glass cylinders (height: 25 cm; diameter: 10 cm; containing 10 cm of water at 24±1 °C) for 6 min (test). A mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only small movements necessary to keep its head above water. The duration of immobility was recorded during the last 4 min of the 6-min testing period.

2.5. Locomotor activity

The assessment of locomotor activity was carried out on mice using a slightly modified method (Li et al., 2004). Briefly, the locomotor activity of the mice was measured by an ambulometer with five activity chambers (JZZ98, Institute of Materia Medica, Chinese Academy of Medical Sciences, China). Mice were placed in the chambers and their paws contacted or disconnected the active bars producing random configurations that were converted into pulses. The pulses, which were proportional to the locomotor activity of the mice, were automatically recorded as the cumulative total counts of motor activity. Mice were placed in test chambers, 15 min prior to the evaluation for acclimatization and then locomotion counts were recorded for a period of 10 min.

2.6. Determination of monoamines and metabolites

Mice were decapitated and their brains were rapidly removed and frozen on dry ice. Various brain areas, including the frontal cortex, hippocampus and striatum, were dissected on a cold plate (−16 °C) according to Franklin and Paxinos (Franklin and Paxinos, 1997). The tissue samples were weighed and stored at −80 °C until homogenization.

The contents of 5-HT, noradrenaline, dopamine, 5-HIAA and DOPAC were measured as described previously (Nitta et al., 1992) using high-performance liquid chromatography (HPLC) with electrochemical detection with minor modifications. Each frozen tissue sample was homogenized by ultrasonication in 200 μl of 0.4 M perchloric acid (solution A). The homogenate was kept on ice for 1 h and then centrifuged at 12,000 ×*g* (4 °C) for 20 min. The pellet was discarded. An aliquot of 160 μl of supernatant was added to 80 μl of solution B (containing 0.2 M potassium citrate, 0.3 M dipotassium hydrogen phosphate and 0.2 M EDTA). The mixture was kept on ice for 1 h and then centrifuged at 12,000 ×*g* (4 °C) for 20 min again. Twenty μl of the resultant supernatant was directly injected into an ESA liquid chromatography system equipped with a reversed-phase C_{18} column (150×4.6 mm I.D., 5μm) and an electrochemical detector (ESA CoulArray, Chelmstord, MA, USA.). The detector potential was set at 50, 100, 200, 300, 400, 500 mV, respectively. The mobile phase consisted of 125 mM citric acid–sodium citrate (pH 4.3), 0.1 mM EDTA, 1.2 mM sodium octanesulfonate and 16% methanol. The flow rate was 1.0 ml/min. The tissue levels of monoamine were expressed in terms of nanograms per gram of tissue.

2.7. Measurements of monoamine oxidase activity

Mice were killed and the brain tissues were rapidly frozen (−80 °C) until analyzed. Mouse brain monoamine oxidase activity was measured following the procedure described previously (Chakrabarti et al., 1998; Krajl, 1965) with a slight modification. Briefly, the brain tissues were homogenized with 4 ml of phosphate buffer (pH 7.4, 0.05 M). The activities of monoamine oxidase-A and -B in brain tissues were measured in the presence of either 1 μM deprenyl (type B inhibitor) or clorgyline (type A inhibitor). For

lysis of the membranes, the tissue homogenate was treated with 0.4 ml of 20% Triton X-100, 2.5 ml of phosphate buffer (pH 7.4) was then mixed with 0.2 ml of the tissue homogenate. The mixture was preincubated at 37 °C for 15 min. Then 30 μl of 2.19 mM kynuramine dihydrobromide was added to the reaction mixture (final concentration 22 μM) as substrate. Samples were then incubated at 37 °C for 30 min again. After incubation, the reaction was terminated by adding 0.2 ml of 5 M perchloric acid. After cooling and centrifugation at 1500 ×*g* for 10 min, an aliquot of 0.5 ml of the supernatant was added to 2.5 ml of 1 M NaOH. The fluorescence intensity was detected with excitation at 315 nm and emission at 380 nm using a fluorescence spectrometer. The concentration of 4-hydroxyquinoline was estimated from a corresponding standard fluorescence curve of 4-hydroxyquinoline. Monoamine oxidase activity was expressed as nmol of 4-hydroxyquinoline formed/30 min/mg protein. Protein concentrations were determined by the method of Bradford (Bradford, 1976).

2.8. Data analysis

Results were expressed as the means ± standard error of the mean (S.E.M.). All data were analyzed statistically using one-way analysis of variance (ANOVA), followed by a post hoc Dunnett's *t*-test. Differences with $P<0.05$ were considered statistically significant.

3. Results

3.1. The effects of curcumin on the duration of immobility in the tail suspension test and forced swimming test

The effects of administration with curcumin were evaluated in two models of depression in mice. Curcumin at the doses of 1.25, 2.5, 5 and 10 mg/kg reduced, in a dose-dependent manner, the duration of immobility in the tail suspension test, resulting in a 16.5%, 31.4%, 45.3% and 52.9% immobility reduction compared with the control group, respectively (Fig. 1). In the forced swimming test, these same doses of curcumin also significantly inhibited immobility with a respective percent reduction of 12.9%, 44.1%, 56.9% and 61.1% (Fig. 2). In both models of depression, the effects of curcumin were similar to those observed for the classical antidepressant imipramine (10 mg/kg, i.p.). The percentages of inhibition for imipramine were 46.5% and 42.9% in the tail suspension and forced swimming tests, respectively (Figs. 1 and 2). Peanut oil and redistilled water were used as control treatments in the preliminary experiment. The behavioral data did not differ between the mice that received the peanut oil and those that received the water. Therefore, we chose to present only the peanut oil control group data for comparison.

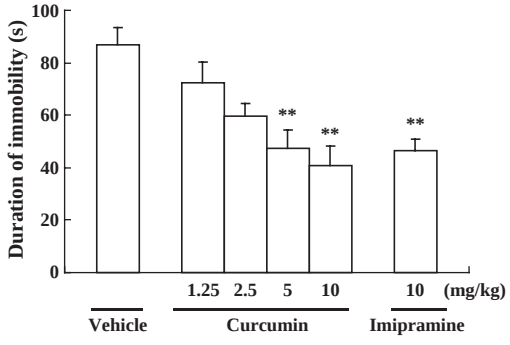

Fig. 1. The effects of curcumin on the duration of immobility in the tail suspension test. Mice were administered vehicle, curcumin (1.25–10 mg/kg) or imipramine (10 mg/kg). The mean immobility time of vehicle animals was 86.8 ± 6.6 s. The respective percent reduction in immobility time was 16.5%, 31.4%, 45.3% and 52.9% for curcumin at 1.25–10 mg/kg and it was 46.5% for imipramine at 10 mg/kg. Values are the mean ± S.E.M. with 15 mice in each group. Data analysis was performed using Dunnett's *t*-test. $^{**}P<0.01$ vs. the vehicle control group.

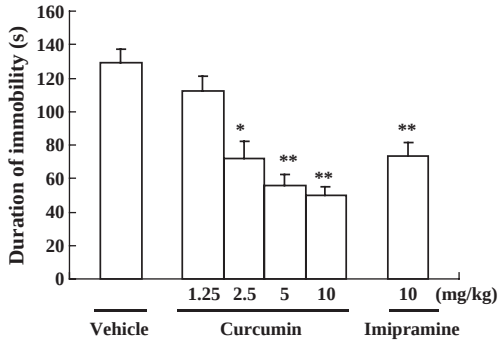

Fig. 2. The effects of curcumin on the duration of immobility in the mouse forced swimming test. Mice were administered vehicle, curcumin (1.25–10 mg/kg) or imipramine (10 mg/kg). The mean immobility time of vehicle animals was 129.2 ± 8.5s. The respective percent reduction in immobility time was 12.9%, 44.1%, 56.9% and 61.1% for curcumin at 1.25–10 mg/kg and it was 42.9% for imipramine at 10 mg/kg. Values are the mean ± S.E.M. with 15 mice in each group. Data analysis was performed using Dunnett's *t*-test. $^{*}P<0.05$, $^{**}P<0.01$ vs. vehicle control group.

3.2. The effects of curcumin on mouse locomotor activity

The effects of curcumin on locomotor activity in mice are shown in Fig. 3. Neither curcumin (2.5 to 10 mg/kg) nor imipramine (10 mg/kg) affected locomotor activity at doses that significantly reduced immobility response in the mouse tail suspension and forced swimming tests.

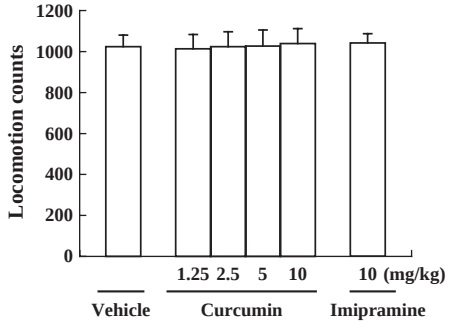

Fig. 3. The effects of curcumin on locomotor activity in mice. Mice were administered vehicle, curcumin (1.25–10 mg/kg) or imipramine (10 mg/kg). The locomotion counts were recorded for 10 min. Values are the mean ± S.E.M. with 15 mice in each group. Data analysis was performed using Dunnett's *t*-test. There were no significant differences compared with the vehicle control group.

Table 1
The effects of curcumin on the concentrations of monoamines and their metabolites in the frontal cortex of mice

Group	Dose (mg/kg)	Frontal cortex (ng/g)					
		5-HT	5-HIAA	5-HIAA/5-HT	Noradrenaline	Dopamine	DOPAC
Control		435.2±20.3	97.0±13.4	0.22±0.02	270.8±23.6	14.4±2.2	22.8±0.8
Curcumin	1.25	435.3±11.0	92.5±6.6	0.21±0.02	278.3±22.9	16.9±3.1	19.1±2.1
	2.5	460.1±31.0	94.4±8.2	0.20±0.01	273.3±11.1	17.3±2.7	21.5±1.9
	5	513.9±19.9	99.9±15.1	0.19±0.03	320.4±13.7	26.2±4.1	21.0±2.9
	10	602.7±21.3[b]	101.7±6.9	0.17±0.01	357.9±12.7[a]	40.4±4.2[b]	20.5±3.2
Imipramine	10	544.7±33.4[b]	90.6±11.3	0.17±0.03	352.1±19.9[a]	19.4±5.0	19.3±1.5

Values are the mean±S.E.M. expressed as nanograms per gram of tissue of 12 animals in each group. Data analysis was performed using Dunnett's *t*-test. [a]$P<0.05$, [b]$P<0.01$, compared with the control group.

3.3. The effects of curcumin on 5-HT, noradrenaline, dopamine and their metabolites in different brain regions of mice

5-HT and noradrenaline levels in the frontal cortex were significantly increased after administration with curcumin (10 mg/kg, p.o.) or imipramine (10 mg/kg, i.p.). Dopamine levels were also increased after administration with 10 mg/kg curcumin only. No significant changes of 5-HIAA or DOPAC levels were seen with either of the two drugs. Both curcumin and imipramine exhibited a tendency for decreased 5-HT turnover (5-HIAA/5-HT) in this region. (Table 1).

As shown in Table 2, an increase in 5-HT levels in the hippocampus was observed following administration with curcumin (5 and 10 mg/kg, p.o.) or imipramine (10 mg/kg, i.p.). The noradrenaline levels were also increased after 10 mg/kg curcumin administration in this region, but not with imipramine. We observed a tendency for decreased 5-HT turnover following the administration of these two drugs.

In the striatum, significantly increased dopamine levels were observed only for curcumin (10 mg/kg), but not for imipramine. No significant changes of 5-HT, dopamine or their metabolites were seen in this brain region after administration of either curcumin or imipramine. (Table 3).

3.4. The effects of curcumin on monoamine oxidase activity in mouse brain

The inhibition of type A and B monoamine oxidase activities by curcumin in mouse brain is shown in Table 4. Sixty min after p.o. administration of curcumin at doses of 1.25 to 10 mg/kg, the mouse brain monoamine oxidase-A (deprenyl-treated) activity was inhibited by 9.5%, 25.7%, 27.4% and 31.1%, respectively. We also found 2.5%, 11.2%, 14.8% and 28.5% inhibition of monoamine oxidase-B (clorgyline-treated) activity at doses of 1.25 to 10 mg/kg. Moclobemide (20 mg/kg) produced monoamine oxidase-A inhibition of 71.0%, but it did not affect monoamine oxidase-B activity.

4. Discussion

It has previously been shown that behavioral studies play an important role in the evaluation of antidepressant drugs. Reduction in the duration of immobility of animals under duress is a behavioral model which reflects the antidepressant properties of these drugs (Wu et al., 1993; Dar and Khatoon, 2000). The tail suspension test and forced swimming test are non-escapable stressful situations and are widely used for screening antidepressive drugs (Karolewicz and Paul, 2001; Junzo et al., 2003). Following the recognition of depressive illness as a biochemical phenomenon, the monoamine hypothesis of depression became widely favored. The present study provides pharmacological and neurochemical evidence for the antidepressant-like activities of curcumin.

Our results demonstrate that curcumin was consistently effective when evaluated in two classical models of depression in mice, the tail suspension and forced swimming tests. In these models, curcumin produced a significant inhibition of the duration of immobility, with a profile comparable to that observed for the classical antidepressant drug imipramine. As changes in the duration of immobility could also result from effects on locomotor activity caused by central nervous system stimulants, the mice were tested in a locomotor activity chamber. These results showed that

Table 2
The effects of curcumin on the concentrations of monoamines and their metabolites in the hippocampus of mice

Group	Dose (mg/kg)	Hippocampus (ng/g)					
		5-HT	5-HIAA	5-HIAA/5-HT	Noradrenaline	Dopamine	DOPAC
Control		532.4±23.6	176.9±14.9	0.34±0.03	245.2±19.5	18.6±4.6	12.3±2.2
Curcumin	1.25	544.0±26.0	175.7±14.0	0.32±0.02	234.5±28.4	20.6±1.7	13.9±3.7
	2.5	554.6±31.8	175.7±11.8	0.32±0.03	245.8±12.2	19.7±3.6	12.3±1.1
	5	664.6±30.9[a]	185.8±13.9	0.28±0.03	321.6±10.7	19.8±5.9	11.5±1.7
	10	712.7±19.6[b]	183.4±14.2	0.25±0.02	373.9±18.3[b]	20.8±5.9	13.2±2.3
Imipramine	10	659.0±33.4[a]	177.9±7.5	0.27±0.02	272.2±23.6	18.2±5.6	15.6±2.3

Values are the mean±S.E.M. expressed as nanograms per gram of tissue of 12 animals in each group. Data analysis was performed using Dunnett's *t*-test. [a]$P<0.05$, [b]$P<0.01$, compared with the control group.

Table 3
The effects of curcumin on the concentrations of monoamines and their metabolites in the striatum of mice

Group	Dose (mg/kg)	Striatum (ng/g)					
		5-HT	5-HIAA	5-HIAA/5-HT	Noradrenaline	Dopamine	DOPAC
Control		626.8±67.1	177.2±19.8	0.29±0.02	88.2±10.0	8076.9±1364.4	778.1±65.5
Curcumin	1.25	650.1±73.2	179.0±17.1	0.28±0.03	89.3±20.9	8059.9±1024.9	750.8±85.9
	2.5	656.8±53.2	179.9±16.9	0.28±0.04	92.1±6.9	8797.0±757.1	764.8±61.7
	5	627.2±39.3	179.8±16.1	0.29±0.05	91.4±16.4	10155.3±1303.9	772.8±65.7
	10	651.2±54.0	180.4±19.5	0.28±0.05	95.8±7.5	12425.2±1003.5[a]	769.3±62.0
Imipramine	10	643.1±24.5	180.8±11.6	0.28±0.02	91.9±10.5	8432.9±714.9	763.7±37.2

Values are the mean±S.E.M. expressed as nanograms per gram of tissue of 12 animals in each group. Data analysis was performed using Dunnett's *t*-test. [a]$P<0.05$, compared with the control group.

curcumin, at doses that produced an antidepressant-like effect, did not significantly change locomotor activity. Therefore, curcumin appears to produce selective antidepressant-like behavioral effects.

It has become clear that depression is a very complex condition that involves abnormalities of the sympathetic nervous system as well as the endocrine and immune systems (Szelenyi and Selmeczy, 2002). However, neurobiological basic research as well as clinical studies have revealed that the monoamines (5-HT, noradrenaline and dopamine) have a crucial role in the development of the depression syndrome. 5-HT may be seen as a crucial 'fine tuner' of normal and pathological processes in addition to having a role as a conventional neurotransmitter. The view that 5-HT has multiple functional roles in depression is supported by clinical and experimental evidence suggesting that serotonin is involved in the regulation of mood, sleep, memory, learning and sexual behavior, all of which are deranged to varying extents in patients with severe depression (Naughton et al., 2000). In addition, Blier and colleagues (1994) have reported that enhancement of 5-HT neurotransmission might underlie the therapeutic response to different types of antidepressant treatment.

In the present study, we focused our attention on three brain regions—the frontal cortex, the hippocampus and the striatum. These brain regions are important because they are involved in important behavioral functions, such as emotion, motivation, learning and memory, all of which may be related to the expression of depression (Butterweck et al., 2002). Our results showed that both curcumin and imipramine mainly affected concentrations of 5-HT in the frontal cortex as well as in the hippocampus. Furthermore, curcumin and imipramine exhibited a tendency for decreasing the 5-HT turnover in both of these brain regions. In most cases, antidepressants such as imipramine induce variable results (may be increased, unchanged or decreased) in 5-HT turnover following acute treatment (Corrodi and Fuxe, 1969; Van Wijk et al., 1977). Moclobemide, an inhibitor of the type A monoamine oxidase activity, yielded an increased level of 5-HT, a concomitant decrease in 5-HIAA and a downward trend in 5-HT turnover (Miura et al., 1996). The present results suggest that the enhanced serotonin level and the downward trend of 5-HT turnover produced by curcumin may be related, at least in part, to an effect on monoamine metabolism.

Table 4
The inhibitory effects of curcumin on type A and type B monoamine oxidase activities in mouse brain

Group	Dose (mg/kg)	Monoamine oxidase-A activity (nmol/30 min/mg protein)	Monoamine oxidase-B activity (nmol/30 min/mg protein)
Control		50.0±0.5	236.7±5.9
Curcumin	1.25	44.3±2.1	230.7±7.5
	2.5	36.4±0.9[b]	210.2±7.7
	5	35.6±0.9[c]	201.6±6.0[a]
	10	34.8±1.6[c]	169.2±7.5[c]
Moclobemide	20	14.2±2.9[c]	223.8±12.7

Monoamine oxidase-A or monoamine oxidase-B activity was determined fluorimetrically using kynuramine as a substrate in the presence of 1 μM deprenyl or clorgyline, respectively. Values are the mean±S.E.M. with 10 mice in each group. Data analysis was performed using Dunnett's *t*-test. [a]$P<0.05$, [b]$P<0.01$ and [c]$P<0.001$, compared with the control group.

Noradrenergic mechanisms are thought to be involved in the control of levels of arousal and consciousness, aggression, anxiety and in reward mechanisms (Montgomery, 1997). Traditional antidepressants, such as the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors, increase the concentration of noradrenaline by either inhibiting neurotransmitter reuptake or inhibiting its degradation. Measurement of noradrenaline after curcumin administration showed that it produced an increase in central noradrenaline concentrations both in the frontal cortex and hippocampus. Judging from the preliminary results that curcumin antagonized the syndromes induced by reserpine, such as ptosis and hypothermia (unpublished results from our laboratory), and it increased the level of noradrenaline present, the antidepressant-like effects of curcumin may be partly due to its influence on the function of adrenergic receptors and/or on the metabolism of noradrenaline.

Although the classical antidepressant drugs are known to interfere mainly with the availability of serotonin and noradrenaline, some studies have suggested that some of their actions are also associated with modulation of dopamine pathways (D'Aquila et al., 2000; Campos et al.,

2004). Such interference with the dopaminergic system could explain, at least in part, the acute effects of some of the antidepressants and also of curcumin. In our study, curcumin increased dopamine levels both in the frontal cortex and striatum, which suggests that the drug influenced the synthesis or metabolism of dopamine to maintain normal dopaminergic function and this might also be involved as a mechanism of antidepressant therapy. However, the extent to which the effect of curcumin in increasing dopamine levels contributes to its antidepressant-like activity needs to be investigated further.

In general, inhibitors of monoamine oxidase cause an increase in the amount of monoamines stored and released from the nerve terminals, thus increasing monoaminergic activity (Dar and Khatoon, 2000). In order to clarify whether the changes of monoamines resulted from the inhibition of monoamine oxidase activity, we assayed mouse brain monoamine oxidase activity after curcumin administration. Monoamine oxidase is classified into types A and B, according to substrate specificity and sensitivity to specific inhibitors (Naoi et al., 1988). Monoamine oxidase-A is inhibited by low concentrations of clorgyline and preferentially oxidizes noradrenaline and 5-HT; whereas monoamine oxidase-B prefers â-phenylethylamine as a substrate, and is inactivated by deprenyl as a selective inhibitor. The inhibitors specific for either type are applied to the treatment of some neuropsychiatric disorders such as depression and schizophrenia (Deniker, 1984). The present study showed that curcumin inhibited both monoamine oxidase types in mouse brain. These findings are in conformity with in vitro studies which show that some dietary-derived food constituents, including curcumin, exhibit monoamine oxidase inhibiting activity (Mazzio et al., 1998). Unlike moclobemide (an inhibitor of type A monoamine oxidase), curcumin inhibited both enzyme forms and increased brain levels of all three neurotransmitters. Although first generation non-selective monoamine oxidase-inhibitors are known to produce the "cheese reaction", a novel brain-selective monoamine oxidase-AB inhibitor, such as TV-3326, was found to be devoid of this "cheese reaction" (Youdim and Weinstock, 2004). The discovery of a new generation of inhibitors, such as short-lasting monoamine oxidase inhibitors, allow for better control of the degree of drug effects and may lead to an improvement of treatment for the many forms of depression. Curcumin is highly lipophilic and should have no trouble entering the central nervous system. Pharmacokinetic studies show that acute oral administration in rats results in a short-lasting activity, due to rapid conversion to glucuronides (Shoba et al., 1998). Because of its long history of use, curcumin may have therapeutic and protective applications in the treatment of depression in the future. However, the efficacy and safety of curcumin at relevant doses need to be established by further study.

Thus, the results of this study showing that curcumin possesses antidepressant properties in behavioral despair tests and that the effects may be related to monoaminergic systems are of great interest. These investigations may add to an understanding of the mechanisms of the antidepressant effects of curcumin. The modified amine theory has suggested that the acute increase in the levels of the monoamines at the synapse may be only an early step in a potentially complex cascade of events that ultimately results in antidepressant activity (Pineyro and Blier, 1999). Considering that clinical antidepressant effects often appear after chronic treatment, the long-term effects of curcumin should be evaluated and further studies should focus on the receptors and signal transduction to elucidate the detailed mechanisms of the antidepressant effect of curcumin.

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