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ORIGINAL INVESTIGATION

Antidepressant activity of curcumin: involvement of serotonin and dopamine system

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Abstract
Rationale Curcumin is a major active principle of *Curcuma longa*, one of the widely used preparations in the Indian system of medicine. It is known for its diverse biological actions.
Objective The present study was designed to investigate the involvement of monoaminergic system(s) in the antidepressant activity of curcumin and the effect of piperine, a bioavailability enhancer, on the bioavailability and biological effects of curcumin.
Methods and observations Behavioral (forced swim test), biochemical (monoamine oxidase (MAO) enzyme inhibitory activity), and neurochemical (neurotransmitter levels estimation) tests were carried out. Curcumin (10–80 mg/kg, i.p.) dose dependently inhibited the immobility period, increased serotonin (5-hydroxytryptamine, 5-HT) as well as dopamine levels (at higher doses), and inhibited the monoamine oxidase enzymes (both MAO-A and MAO-B, higher doses) in mice. Curcumin (20 mg/kg, i.p.) enhanced the anti-immobility effect of subthreshold doses of various antidepressant drugs like fluoxetine, venlafaxine, or bupropion. However, no significant change in the anti-immobility effect of imipramine and desipramine was observed. Furthermore, combination of subthreshold dose of curcumin and various antidepressant drugs resulted in synergistic increase in serotonin (5-HT) levels as compared to their effect per se. There was no change in the norepinephrine levels. The coadministration of piperine (2.5 mg/kg, i.p.), a bioavailability enhancing agent, with curcumin (20 and 40 mg/kg, i.p.) resulted in potentiation of pharmacological, biochemical, and neurochemical activities.
Conclusion The study provides evidences for mechanism-based antidepressant actions of curcumin. The coadministration of curcumin along with piperine may prove to be a useful and potent natural antidepressant approach in the management of depression.

Keywords Curcumin · Forced swim test (FST) · Serotonin · Monoamine oxidase (MAO) · Piperine

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Introduction

Curcumin, a major active component of *Curcuma longa*, has been used since time immemorial. Traditionally, it is used as a condiment to give distinctive flavor to the curry. Curcumin is known for its diverse biological actions, such as antioxidant (Sreejayan and Rao 1994), anti-inflammatory (Ammon and Wahl 1991; Brouet and Ohshima 1995; Dikshit et al. 1995), anticarcinogenic, antimicrobial (Limtrakul et al. 1997; Kiso et al. 1983; Rao et al. 1995), hepatoprotective (Kiso et al. 1983), hypoglycemic (Srinivasan 1972; Babu and Srinivasan 1995; Arun and Nalini 2002), thrombosuppressive (Srivastava et al. 1985), and antiarthritic (Deodhar et al. 1980). In spite of the high efficacy and safety, curcumin has yet not been approved as a therapeutic agent and perhaps more so because of its poor bioavailability. It has poor absorption rate and it undergoes rapid metabolism which severely curtail the bioavailability. Curcumin has been reported to possess antidepressant-like effects in animal

models commonly employed for the prediction of antidepressant activities (Xu et al. 2005a, b; Kulkarni and Mehta 1985; Porsolt et al. 1978). Chronic administration of curcumin has been reported to exert antidepressant-like action in olfactory bulbectomy model of depression in rats (Xu et al. 2005b). More recently, these investigators have reported the involvement of 5-hydroxytryptamine $(5\text{-HT})_1$ and 5-HT_2 receptors in the antidepressant action of curcumin (Wang et al. 2008). However, the exact mechanism of its antidepressant activity still remains to be explored.

Keeping in view of monoaminergic theories of mental depression, the present study was designed to investigate the involvement of catecholaminergic and serotonergic (5-HT) systems and monoamine oxidase (MAO) enzyme system(s) in the antidepressant activity of curcumin employing behavioral (forced swim test, FST), biochemical, and neurochemical approaches. Attempts have also been made to study the effect of piperine, a bioavailability enhancer, on the bioavailability of curcumin and thereby its biological effects.

Materials and methods

Animals

Male Laca mice (24–30 gm) bred at Central Animal House, Panjab University, Chandigarh, were used. The animals were housed under standard (25±2°C, 60–70% humidity) laboratory conditions, maintained on a 12-h light and dark cycle, with free access to standard food and water. Animals were acclimatized to laboratory conditions before the test. All behavioral experiments were carried out between 1,000 and 1,400 h. The experimental protocols were approved by the Institutional Animal Ethical Committee and conducted according to the Committee for the Purpose of Control and Supervision on Experiments on Animals guidelines on the use and care of experimental animals.

Forced swim test

The animals were individually forced to swim in a measuring cylinder (20 cm high, 10 cm in diameter) filled with water (23–25°C) up to a height of 15 cm (Xu et al. 2005a, b). After the initial 2–3 min of vigorous activity, the animals showed period of immobility by floating with minimum movements. An animal was considered to be immobile whenever it remained floating passively in the water in a slightly hunched but upright position, its nose above the water surface. The total immobility period during the 6-min test was recorded with the help of a stopwatch (Kulkarni and Mehta 1985).

Measurement of locomotor activity

Locomotor activity (ambulations) was measured by using an actophotometer (IMCORP, India). Briefly, mice were allowed to acclimatize to the observation chamber for a period of 2 min. Locomotion was expressed in terms of total number of ambulations (total photobeams counts) during a 5-min test for each mouse (for details, see Dhir et al. 2005).

Measurement of monoamine oxidase enzyme activity

The MAO activity was assessed spectrophotometrically (Schurr and Livne 1975). Mice were decapitated and brains were removed on ice pack. The buffer-washed brain samples were homogenized in 10 volume of sodium phosphate buffer (0.1 M, pH 7.4) and centrifuged (Biofuge primo-R, Germany) at 15,000×*g* for 20 min. Supernatant were pipetted out and used for the estimation of MAO-A and MAO-B activity. Pellets were discarded. For estimating MAO-A activity, 2.75 ml Tris buffer (0.1 M, pH 7.4) and 100 μl of 4 mM 5-hydroxytryptamine were mixed in quartz cuvette which was then placed in double beam spectrophotometer (UV-Pharmaspec-1700, Shimadzu, Japan). This was followed by the addition of 150 μl solution of brain homogenate to initiate the enzymatic reaction and the change in absorbance was recorded at wavelength of 280 nm for 5 min against the blank. For estimating MAO-B activity, 2.75 ml Tris buffer (0.1 M, pH 7.4) and 100 μl of 0.1 M benzylamine were mixed in quartz cuvette which was then placed in double beam spectrophotometer. This was followed by the addition of 150 μl solution of brain homogenate to initiate the enzymatic reaction and the change in absorbance was recorded at wavelength of 249.5 nm for 5 min against the blank containing Tris buffer and 5-hydroxytryptamine.

High pressure liquid chromatography studies

Measurement of biogenic amines

Biogenic amines (norepinephrine, serotonin, and dopamine) were estimated by high pressure liquid chromatography (HPLC) with electrochemical detector by the method of Beyer et al. 2002. Waters® standard system consisting of a high pressure isocratic pump, a 20-μl sample injector valve, C18 reverse phase column, and electrochemical detector were used. Data were recorded and analyzed with the help of Empower® software. Mobile phase consisting of 0.15 M sodium dihydrogen phosphate, 0.25 mM ethylenediaminetetraacetic acid, 1.75 mM 1-octane sulfonic acid, 2% isopropanol, and 10% methanol (pH 4.8). Electrochemical conditions for the experiment were +0.800 V, sensitivity

ranges from 1–100 nA. Separation was carried out at a flow rate of 1 ml/min. Samples (20 μl) were injected manually. Brain samples were homogenized in a homogenizing solution containing 0.1 M perchloric acid. After that, samples were centrifuged at 24,000×*g* for 15 min. The supernatant was further filtered through 0.25-μm nylon filters before injecting in the HPLC injection pump.

Estimation of curcumin levels in brain

Mice were decapitated and brains were removed. The buffer-washed brain samples were homogenized in 10 volume of sodium phosphate buffer (0.1 M, pH 3) and centrifuged at 15,000×*g* for 20 min. Pellets were discarded and supernatant were pipetted out. Supernatant were then extracted with methanol in a ratio of 1:1 *v*/*v* and centrifuged at 10,000×*g* for 15 min. Curcumin levels were estimated by reverse phase high pressure liquid chromatography using a modification of the method described by Lao et al. (2006). HPLC conditions were mobile phase of acetonitrile/methanol/10% acetic acid (30:60:10 *v*/*v*/*v*), at a flow rate of 1.2 ml/min; column: water spherisorb (C_{18}, 4.6×250 mm, 5 μm; UV detection at 420 nm). Curcumin detection was found to be linear with in range of 0.0156–0.125 μg/ml, with a detection limit of 0.0156 μg/ml.

Drugs and treatment protocols

The following drugs were used: curcumin (Sanat Products Ltd, Delhi, India), fluoxetine (Eli Lilly and Co., USA), venlafaxine (Panacea Biotec Ltd, New Delhi, India), imipramine (Ciba-Geigy, USA), desipramine (Sigma Aldrich, St. Louis, MO, USA), bupropion (GlaxoSmithKline Beecham, PA, USA), tranylcypromine (SmithKline and French Labs., PA, USA), selegiline, reserpine, and piperine. All the drugs were dissolved in distilled water except reserpine, curcumin, and piperine. Reserpine was dissolved with the help of a few drops of acetic acid and the volume was made up with distilled water, whereas curcumin and piperine were dissolved in rice bran oil. The doses of the drugs used were selected according to the previous studies conducted in our laboratory (Dhir et al. 2005; Kulkarni and Mehta 1985) and as reported in the literature (Xu et al. 2005a, b). All the drugs were administered intraperitoneally in a fixed volume of 1 ml/100 g body weight. The drugs were administered 60 min before the animals were subjected to different tests (behavioral, biochemical, and neurochemical). Fluoxetine, venlafaxine, imipramine, desipramine, bupropion, tranylcypromine, and selegiline were administered 30 min before the test. Reserpine was given 4 h before challenging the animal to FST.

In a separate series of experiments, we investigated the effect of coadministration of curcumin on the antidepressant action of other drugs such as fluoxetine (selective serotonin reuptake inhibitor), venlafaxine (dual reuptake inhibitors of serotonin and norepinephrine), imipramine (a first generation antidepressant drug), desipramine (selective norepinephrine modulator), bupropion (dopamine reuptake inhibitor), tranylcypromine (monoamine oxidase-A inhibitor), and selegiline (selective monoamine oxidase-B inhibitor). To this end, mice were pretreated with curcumin (20 mg/kg, i.p.) or saline, and after 30 min, they received the respective drugs, i.e., fluoxetine (5 mg/kg, i.p.), venlafaxine (4 mg/kg, i.p.), imipramine (5 mg/kg, i.p.), desipramine (5 mg/kg, i.p.), bupropion (5 mg/kg, i.p.), tranylcypromine (5 mg/kg, i.p.), and selegiline (5 mg/kg, i.p.). The animals were thereafter subjected to different behavioral (FST), biochemical (MAO enzyme activity), and neurochemical (monoamine levels) tests 30 min post-antidepressant drug administration. For studying the effect of piperine on the bioavailability of curcumin, mice were coadministered a subthreshold dose of piperine (2.5 mg/kg, i.p.) and curcumin (20 mg/kg, i.p.), respectively.

Statistical analysis

One specific group of mice was assigned to one specific drug treatment condition and each group comprised six mice (n=6). All the values are expressed as means± standard error of the mean. The data were analyzed by one-way analysis of variance followed by Tukey's test. $p \leq 0.05$ was considered as statistically significant.

Results

Effect of curcumin on FST and reserpine-induced immobility period

Curcumin (10–80 mg/kg, i.p.) showed dose-dependent decrease in the immobility period as compared to vehicle-treated group in FST (Fig. 1a). The maximum anti-immobility response was observed 60 min post-curcumin (40 mg/kg, i.p.) administration (Fig. 1b). Curcumin (40 and 80 mg/kg, i.p.) significantly reversed reserpine-induced immobility period (Fig. 1c). Curcumin (10–80 mg/kg, i.p.) did not produce any significant change in the ambulatory movements of the animal (result not shown).

Effect of combination of subthreshold dose of curcumin (20 mg/kg, i.p.) with subthreshold dose of other antidepressants (venlafaxine, fluoxetine, imipramine, desipramine, and bupropion) on immobility period

Venlafaxine (4–16 mg/kg, i.p.), fluoxetine (5–20 mg/kg, i.p.), imipramine (5–20 mg/kg, i.p.), desipramine (5–20 mg/kg,

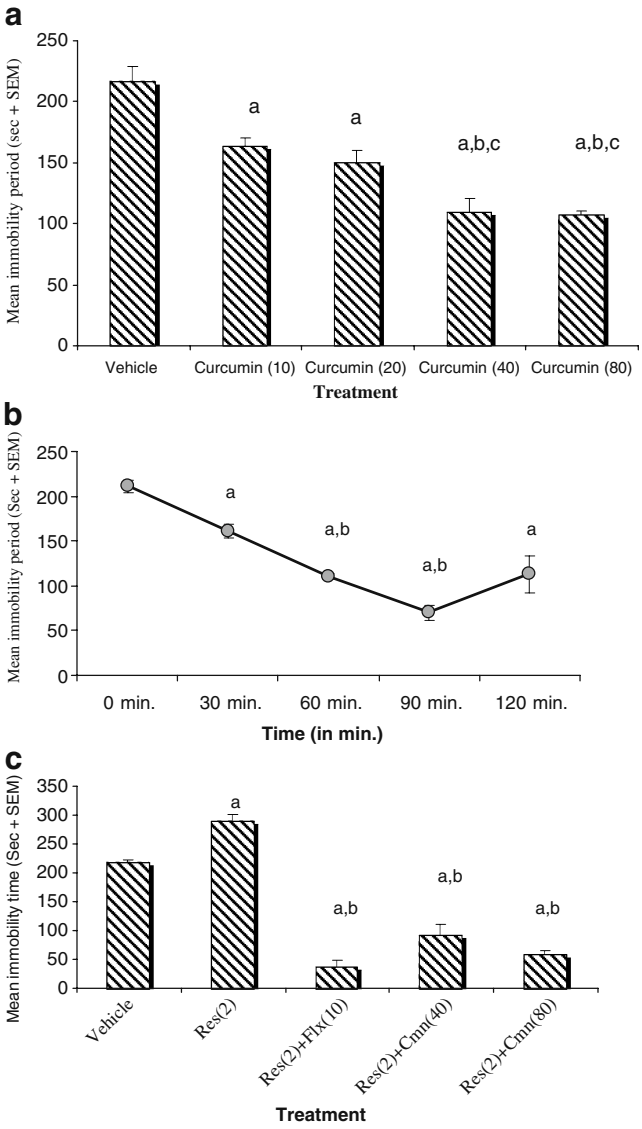

Fig. 1 Effect of increasing doses of curcumin on forced swim- and reserpine-induced immobility period in mice. **a** *a* $p \leq 0.05$ as compared with vehicle group; *b* $p \leq 0.05$ as compared with curcumin (10); *c* $p \leq 0.05$ as compared with curcumin (20). **b** *a* $p \leq 0.05$ as compared to 0 min; *b* $p \leq 0.05$ as compared to 30 min. **c** *a* $p \leq 0.05$ as compared with vehicle group; *b* $p \leq 0.05$ as compared with reserpine (2)

i.p.), and bupropion (5–20 mg/kg, i.p.) showed dose-dependent anti-immobility effect in FST (Fig. 2a,b). When subthreshold dose of venlafaxine (4 mg/kg, i.p.), fluoxetine (5 mg/kg, i.p.), and bupropion (5 mg/kg, i.p.) was combined with subthreshold dose of curcumin (20 mg/kg, i.p.), the antidepressant activity was potentiated as compared to the effect per se of curcumin or the corresponding drug (Fig. 2c), whereas coadministration of curcumin (20 mg/kg, i.p.) with desipramine (5 mg/kg, i.p.) and imipramine (5 mg/kg, i.p.) did not show potentiation in the anti-immobility effect per se of curcumin or the other two drugs (Fig. 2d).

Effect of combination of subthreshold dose of curcumin (20 mg/kg, i.p.) with subthreshold dose of MAO inhibitors on immobility period

Tranylcypromine, nonspecific MAO inhibitor (2.5–10 mg/kg, i.p.), and selegiline, selective MAO-B inhibitor (5–10 mg/kg, i.p.), showed dose-related reduction in the immobility period as compared to vehicle-treated group in FST. On combining the subthreshold dose of MAO inhibitors, tranylcypromine (5 mg/kg, i.p.), and selegiline (5 mg/kg, i.p.), with subthreshold dose of curcumin (20 mg/kg, i.p.), there was a potentiation in the antidepressant activity as compared to effect per se of curcumin or the corresponding drug (Fig. 3).

Effect of curcumin on monoamine oxidase enzyme activity

Curcumin, in a dose range of 20–80 mg/kg, i.p., showed dose-dependent inhibition in MAO-A enzyme activity. Even though curcumin significantly inhibited the MAO-B enzyme activity, the effect was not dose dependent (Fig. 4).

Effect of curcumin and its combination with other antidepressant drugs on brain monoamine levels

Curcumin (20–80 mg/kg, i.p.) treatment led to an increase in the serotonin (5-HT) levels. Dopamine levels were also found to be increased but only at high doses. However, there was no significant change in the levels of brain norepinephrine observed (Fig. 5a). Subthreshold doses of other antidepressants (venlafaxine 4 mg/kg, i.p; fluoxetine 5 mg/kg, i.p.; and bupropion 5 mg/kg, i.p.) did not produce any change in the brain monoamine levels. When subthreshold dose of serotonin modulating agents was combined with subthreshold dose of curcumin (20 mg/kg, i.p.), there was significant increase in the 5-HT levels with respect to vehicle control and effect per se of the drug (Fig. 5b–d). These combinations did not produce any change in dopamine and norepinephrine levels.

Effect of coadministration of piperine and curcumin on immobility period, monoamine oxidase activity, and brain monoamine levels

Piperine at lower doses (1 and 2.5 mg/kg, i.p.) did not produce any anti-immobility effect, but higher doses (5 and 10 mg/kg, i.p.) showed effect per se in the FST. When piperine (2.5 mg/kg, i.p) was combined with curcumin (20 mg/kg, i.p.), a significant potentiation (62%) was observed in the anti-immobility activity of curcumin (20 mg/kg, i.p) per se. The effect of combination of curcumin (20 mg/kg,

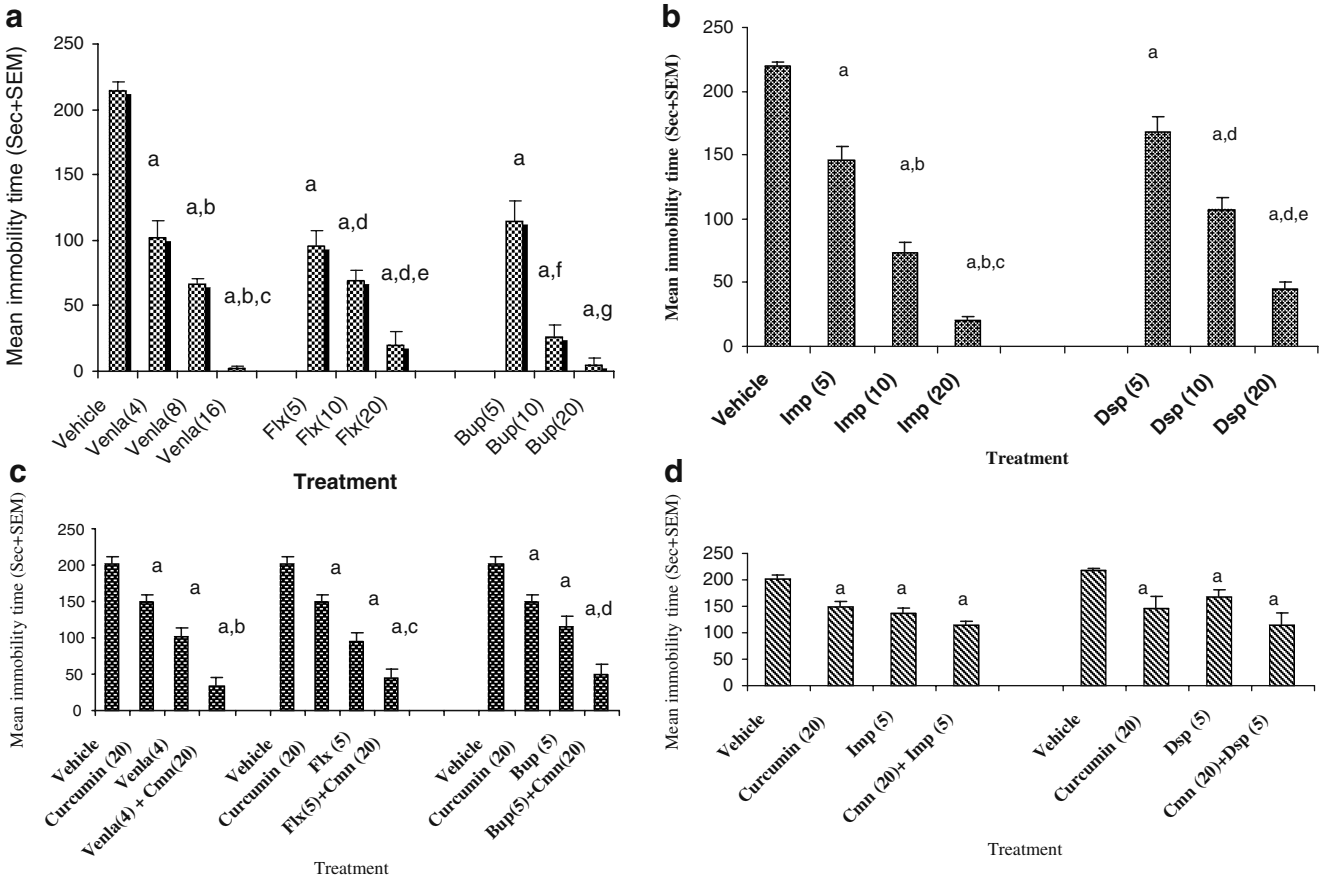

Fig. 2 Effect of combination of subthreshold dose of curcumin (20 mg/kg., i.p.) with subthreshold doses of known antidepressants (venlafaxine, fluoxetine, imipramine, desipramine, and bupropion) on immobility period. **a** *a* $p \leq 0.05$ as compared with vehicle group; *b* $p \leq 0.05$ as compared with venlafaxine (4); *c* $p \leq 0.05$ as compared with venlafaxine (8); *d* $p \leq 0.05$ as compared with fluoxetine (5) ; *e* $p \leq 0.05$ as compared with fluoxetine (10); *f* $p \leq 0.05$ as compared with bupropion (5); *g* $p \leq 0.05$ as compared with bupropion (10). **b** *a* $p \leq 0.05$ as compared with vehicle group; *b* $p \leq 0.05$ as compared with imipramine (5); *c* $p \leq 0.05$ as compared with imipramine (10); *d* $p \leq 0.05$ as compared with desipramine (5); *e* $p \leq 0.05$ as compared with desipramine (10). **c** *a* $p \leq 0.05$ as compared with vehicle group; *b* $p \leq 0.05$ as compared with curcumin (20) and venlafaxine (4); *c* $p \leq 0.05$ as compared with curcumin (20) and fluoxetine (5); *d* $p \leq 0.05$ as compared with curcumin (20) and bupropion (5). **d** *a* $p \leq 0.05$ as compared with vehicle group

i.p.) and piperine was similar to curcumin (40 mg/kg, i.p.) alone. The combination of curcumin (20 mg/kg, i.p) and piperine (2.5 mg/kg, i.p) produced significant potentiation (64%) in the MAO-A enzyme inhibitory activity of curcumin (20 mg/kg, i.p) per se and this effect was comparable with curcumin (40 mg/kg, i.p) alone. However, this combination did not potentiate the MAO-B enzyme inhibitory activity of curcumin (20 mg/kg, i.p) per se. Piperine (2.5 mg/kg, i.p.) did not produce any change in the brain monoamine levels. When curcumin (20 mg/kg, i.p.) and piperine (2.5 mg/kg, i.p.) were coadministered, a significant increase in the 5-HT levels (35%) was observed as compared to effect per se of subthreshold doses. The increase in the levels of 5-HT observed was comparable to that of curcumin (40 mg/kg, i.p.) per se response (results not shown). Coadministration of piperine (2.5 mg/kg, i.p.) and curcumin significantly increased the brain levels of curcumin (results not shown).

Discussion

This study provides pharmacological, biochemical, and neurochemical evidences for the involvement of monoamines particularly serotonin and MAO-A enzyme system in the antidepressant-like effect of curcumin. Our results demonstrated a consistent antidepressant-like activity of curcumin in two classical models of depression in mice, namely the forced swim and reserpine-induced immobility models. In FST, curcumin dose dependently inhibited the immobility period, the maximum anti-immobility effect reached at 60-min postdrug administration. Route of administration did not result in significant change in antidepressant effect of curcumin. The decrease in immobility period observed was independent of its locomotor activity as curcumin, at doses that produced antidepressant-like effect, did not produce any significant change in the

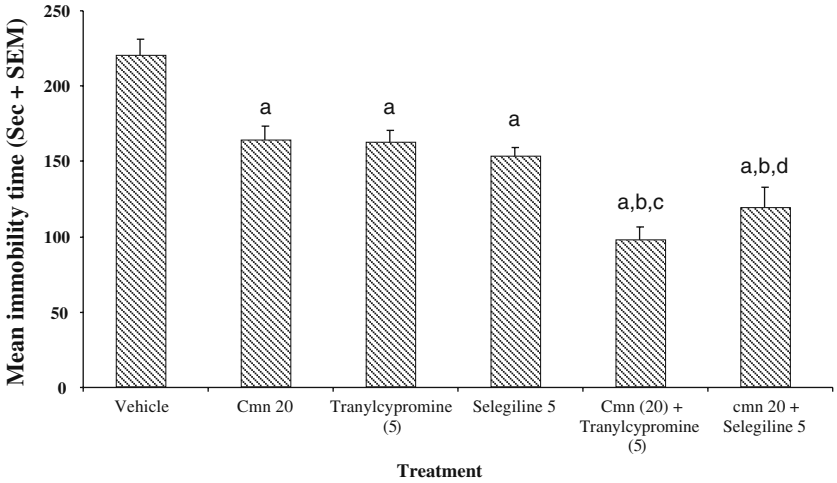

Fig. 3 Effect of combination of subthreshold dose of curcumin (20 mg/kg, i.p.) with subthreshold dose of monoamine oxidase inhibitors on immobility period. *a* $p \leq 0.05$ as compared with vehicle group; *b* $p \leq 0.05$ as compared with curcumin (20); *c* $p \leq 0.05$ as compared with tranylcypromine (5); *d* $p \leq 0.05$ as compared with selegiline (5)

locomotor activity. Similar observations have been reported by Xu et al. (2005a) earlier.

Neurobiological evidences both in animal and in human have indicated the role of monoaminergic systems (catecholamines and serotonin) in the pathophysiology of mental depression (Elhwuegi 2004). Consistent with this view, most antidepressive drugs exerted their action by elevating synaptic monoamine concentrations (Schloss and Henm 2004). In our study, when the subthreshold dose of curcumin (20 mg/kg, i.p.) was coadministered with subthreshold dose of serotonin-modulating drugs such as venlafaxine (4 mg/kg, i.p.) and fluoxetine (5 mg/kg, i.p.), there was a potentiation in the antidepressant effect of these agents as compared to their effects per se. The neurochemical analysis revealed that curcumin (20–80 mg/kg, i.p.) dose dependently increased the serotonin (5-HT) levels. It also increased the levels of dopamine but the effect was observed only at higher doses. There was no change in the levels of brain norepinephrine. The combination of subthreshold dose of serotonin-modulating agents and curcumin showed an increase in serotonin (5-HT) levels as compared to their effect per se. These studies support the serotonergic involvement in the antidepressant-like activity of curcumin (Xu et al. 2005a, b). Wang et al. (2008) have suggested the involvement of serotonin receptors (5-HT_1 and 5-HT_2) in the antidepressant-like effect of curcumin. Serotonin is considered as a "fine tuner" of normal and pathological processes in addition to its conventional role of a neurotransmitter. The view that 5-HT has multiple functional roles in depression is supported by the clinical and experimental evidences suggesting that the neurotransmitter (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 mental depression (Naughton et al. 2000). Blier and De Montigny (1994) have argued that enhancement of

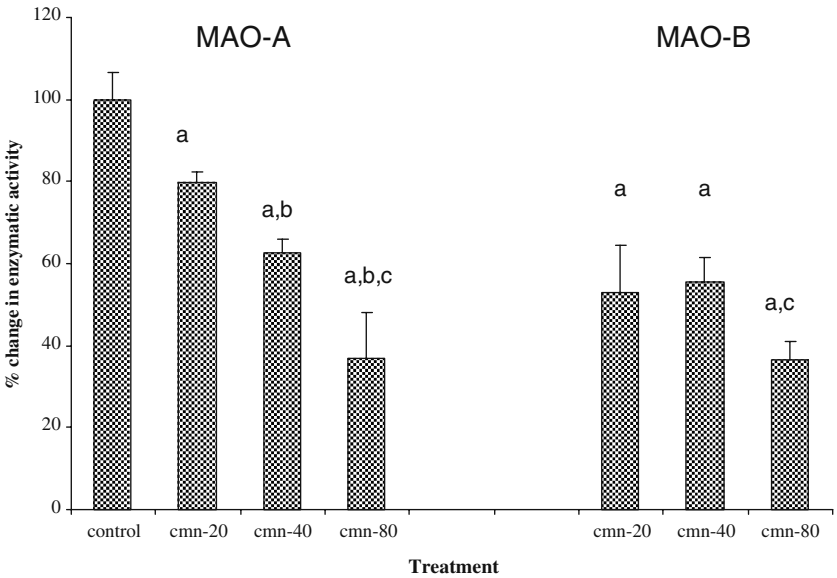

Fig. 4 Effect of curcumin on monoamine oxidase enzyme (*MAO*) activity. *a* $p \leq 0.05$ as compared with vehicle group; *b* $p \leq 0.05$ as compared with curcumin (20); *c* $p \leq 0.05$ as compared with curcumin (40)

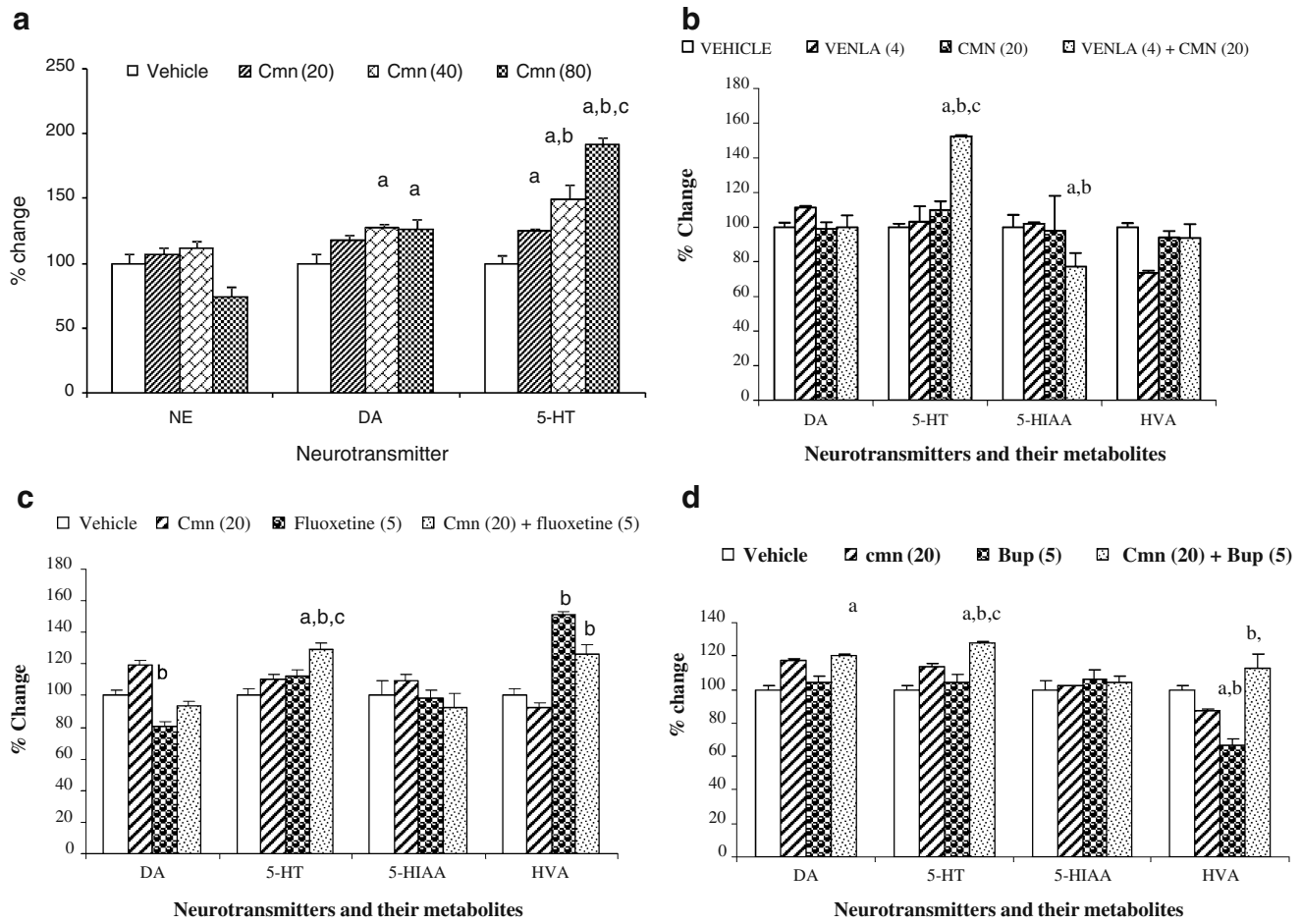

Fig. 5 Effect of curcumin, other antidepressants, and their combinations on brain neurotransmitter levels. **a** *a* $p \leq 0.05$ as compared with vehicle group; *b* $p \leq 0.05$ as compared with curcumin (20); *c* $p \leq 0.05$ as compared with curcumin (40). **b** *a* $p \leq 0.05$ as compared with vehicle group; *b* $p \leq 0.05$ as compared with venlafaxine (4); *c* $p \leq 0.05$ as compared with curcumin (20). **c** *a* $p \leq 0.05$ as compared with vehicle group; *b* $p \leq 0.05$ as compared with curcumin (20); *c* $p \leq 0.05$ as compared with fluoxetine (5). **d** *a* $p \leq 0.05$ as compared with vehicle group; *b* $p \leq 0.05$ as compared with curcumin (20); *c* $p \leq 0.05$ as compared with bupropion (5)

5-HT neurotransmission might underlie the therapeutic response to different types of antidepressant treatment. It appears, therefore, that increase in the levels of serotonin is critical to the antidepressant activity of curcumin.

Even though Serra et al. (1979) proposed the involvement of dopaminergic presynaptic receptors in the action of antidepressants a long back, it was not considered as one of the accepted theories of mental depression. Our recent studies have reported the implication of dopamine as one of the important targets in the action of antidepressant drugs (Dhir and Kulkarni 2007). In the present study, when curcumin was coadministered with bupropion or selegiline, it potentiated the antidepressant activity of both the drugs. Neurochemically, curcumin also significantly increased the brain dopamine levels (at higher doses). It also inhibited MAO-B enzyme activity suggesting that increase in dopamine levels may be due to its MAO-B enzyme inhibiting property. It is of interest that curcumin neither potentiated the antidepressant profile of first generation antidepressants like imipramine or desipramine in behavioral observations nor neurochemically when brain norepinephrine levels were investigated.

In general, inhibitors of monoamine oxidase enzyme cause an increase in the content of neuronal monoamines, thus increasing monoaminergic activity (Dar and Khatoon 2000). In order to verify whether the curcumin had monoamine oxidase enzyme inhibitory property or not, the experiments conducted revealed that curcumin dose dependently inhibited MAO-A activity, whereas MAO-B inhibitory activity was observed only at higher doses. The enhanced brain levels of serotonin observed following the curcumin administration may be related to the inhibition of MAO-A enzyme. This was supported by the combination studies where subthreshold dose of curcumin potentiated the effect of a subthreshold dose of tranylcypromine in FST. The in vitro studies have shown that some dietary-derived food constituents, including curcumin, exhibit monoamine oxidase inhibiting activity (Mazzio et al. 1998); furthermore,

Xu et al. (2005a) have reported the MAO inhibitory activity of curcumin in vivo studies as well.

Based on the present observations, curcumin, at low doses, increased brain serotonin levels via inhibiting its metabolism (MAO-A enzyme inhibition) without significantly affecting the levels of norepinephrine. At high doses, it inhibited the metabolism of dopamine (MAO-B enzyme inhibition) which in turn resulted in the increase in central dopamine levels. Both these activities of curcumin, i.e., by enhancing the availability of serotonin and dopamine in the brain, are responsible for its antidepressant activity.

The bioavailability of curcumin is a major concern which limits its therapeutic utility. Piperine, a known inhibitor of hepatic and intestinal glucuronidation, when coadministered with curcumin, increased the bioavailability of curcumin (Shoba et al. 1998) and thereby its pharmacological and biochemical activities. Neurochemically, there was not only many fold increase in brain 5-HT levels but also in brain curcumin levels (results not shown).

In conclusion, curcumin exerted antidepressant-like effects in behavioral despair paradigm in mice through the central monoaminergic system, mainly enhancing the serotonergic and dopaminergic (at higher doses) synaptic availability. Also, the coadministration of curcumin and piperine may provide a useful natural adjuvant in the antidepressant therapy.

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