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Effect of curcumin on quinpirole induced compulsive checking: An approach to determine the predictive and construct validity of the model

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Abstract

Background: Disorders of anxiety vary in severity to a wide extent, and obsessive-compulsive disorder (OCD) persists as the fourth most common form of mental illness and is reported to be associated with memory impairment, necessitating effective means of treatment. **Aim**: To study the effect of curcumin on OCD. **Methods**: The present study includes the determination of effect of curcumin at 5 and 10 mg/kg in quinpirole (0.5 mg/kg) -induced model of OCD, memory retention and brain monoamine levels in rats. **Results**: A significant improvement from the obsessive-compulsive symptoms induced by quinpirole was observed in curcumin treated rats; curcumin showed a protective effect on memory task. An increase in serotonin levels and a decrease in the dopamine levels were observed in curcumin treated rats. **Conclusion**: Curcumin treatment had shown a protective effect in OCD with considerable influence on brain monoamine levels, thus providing an evidence for the predictive and construct validity of the model.

Keywords: Obsessive-compulsive disorder, curcumin, quinpirole, water maze apparatus, dopamine, serotonin.

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Introduction

Anxiety disorders are prevailing to be the major central nervous system disorders in the community, of which obsessive-compulsive disorder (OCD) is considered to be the fourth most common form of mental illness. It is reported that 1 out of every 40 people suffer with this disorder, approximating 2.5% of the world population [1]. OCD, a chronic illness considered as one of the ten leading causes of disability with severity of symptoms varying in intensity overtime and impairing quality of life [2], is characterized by obsessions such as recurrent, persistent unwanted thoughts, impulses or images that are experienced as intrusive and inappropriate for which compulsions, such as repetitive behavior or mental acts, are performed in response [3].

The principal loci of pathological changes are reported to be in the orbitofrontal cortex (OFC), anterior cingulate gyrus (ACG) and basal ganglia, of which OFC and ACG communicate with the basal ganglia [4]. These structures are involved in detection of errors in brain circuits. Various theories of occurrence of OCD suggest that excessive stimulation of OFC and ACG result in generation of excessive, erroneous messages to the basal ganglia [5]. In turn, general memory deficit [6] and reduced memory confidence [7] are attributed to obsessive-compulsive patients in one hypothesis. Various neurotransmitters are clearly indicated to have a pivotal role in the etiology of OCD, of which involvement of serotonergic system [8, 9] is of primary importance. Hence, the pharmacotherapy of OCD is mainly achieved with selective serotonin reuptake inhibitors (SSRIs) [10]. Though efforts to elucidate the

neurobiology of OCD have centred largely on the role of serotonin for the past two decades, involvement of norepinephrine and dopaminergic systems are also reported to play an important role in its pathogenesis [11, 12].

Curcumin, the major active constituent of curcuma longa, has been reported in our previous studies to have an influential role on serotonin, norepinephrine and dopamine in various regions of brain, and it is observed to be beneficial in various central nervous system (CNS) disorders like depression [13] and epilepsy [14]. Apart from enhancing the levels of various biogenic amines, it is also reported to inhibit their degradation by inhibiting MAO-A and B in brain [15]. The involvement of these monoamines, primarily in the etiology of OCD, and curcumin's potential to increase the monoamine levels has led to the evaluation of the effect of curcumin in the treatment of OCD using quinpirole-induced compulsive checking [16]. The effect of OCD on acquired memory was studied using Morris water maze task of spatial learning [17]. The effect of quinpirole and curcumin on brain monoamine levels were studied to elucidate the mechanism involved, which also helps in determining the predictive validity of the model. Moreover, the existing treatment for OCD entails long-term use of SSRIs and other antidepressants that are associated with varied side effects such as loss of libido, nervousness, insomnia, anorexia, dyskinesia, etc. [18] Hence, curcumin could be an effective natural alternative devoid of side effects in the treatment of OCD and associated memory disturbances.

Materials and Methods

Animals

Inbred Adult Wistar rats (200-250 g) were procured from the animal house of Bapatla College of Pharmacy (1032/ac/07/CPCSEA), Bapatla, India, and were housed at a constant room temperature of 22 ± 1 ºC, 40-50% relative humidity and 12 h light/dark cycles. Standard pellet feed (Rayan's Biotech, Hyderabad) and water was provided *ad libitum* throughout the experimentation period. Animals were acclimatized to laboratory conditions one week prior to initiation of experiments. The experimental protocol was approved by Institutional animal ethics committee (IAEC/I-6/BCOP/2007-2008) and all the experiments involved in this work were performed in accordance with CPCSEA guidelines for the use and care of experimental animals.

Drugs and drug administration

Curcumin was procured from chemiloids, Laila Impex, Vijayawada and characterized using H+ NMR studies. For oral administration, curcumin was mixed with peanut oil and diluted to the desired concentration with the same on the day of administration. Paroxetine 1.8 mg/kg, p.o. was suspended in 1% carboxy methyl cellulose (CMC). The peanut oil and CMC were used as control treatments. Since the behavioral data did not differ between rats that received these vehicles, peanut oil (vehicle) treated group is considered as control.

Training of rats for spatial learning

All the rats were trained to swim individually in Morris water maze [19] that consists of circular water tank with a diameter of 100 cm and depth of 20 cm containing water at 25 °C rendered opaque by adding milk powder. A platform (diameter 4.5 cm; height 19 cm) was submerged 1 cm below the water surface and at the centre of one quadrant. Each quadrant had a starting point, where the rats were placed in the maze and allowed to find the escape platform hidden under the water for 60-90 sec. Each day, 2-4 trials were performed for 4-5 days until the latency to reach the escape platform was markedly reduced.

Grouping of animals

Rats were randomly assigned to 5 groups after training for spatial learning. Group I rats were treated with peanut oil 0.1 ml/100 mg and served as control; group II rats served as negative control; group III, group IV and group V rats were treated with 5 mg/kg, 10 mg/kg of curcumin and paroxetine 1.8 mg/kg p.o., respectively, for 35 days. Quinpirole 0.5 mg/kg p.o. was administered to all the groups except control, twice in a week and 1 h before exposure to the open field on the last day of treatment.

Quinpirole-induced compulsive checking

Compulsive checking induced with quinpirole was tested by placing the rats individually on a large open field that consists of four objects with different shapes and colors fixed equidistantly at four corners of a flat wooden board. After 35 days of treatment with drugs, rats of each group were analyzed individually to obtain the behavioral measures such as: 1) Frequency of stops in each locale, 2) Total duration of stopping in a given locale, 3) Number of visits to other objects in between returns to a given locale, 4) Occurrence and frequency of occurrence of ritualistic behavior at various objects were observed and recorded for a period of 55 min [20]. The open field was thoroughly cleaned to deodorise it after each observation.

Memory

After the behavioral measurements in quinpirole-induced compulsive checking, rats of different groups were placed individually in the water maze to evaluate the effect of different treatments on retention of acquired task of identification of hidden platform under water. The latency to reach the hidden platform was observed, and after a cut-off time of 90 sec, the rats were returned to the cage.

Estimation of rat brain dopamine and serotonin levels

Rats were sacrificed by cervical dislocation and the brains were isolated quickly. Anesthesia was not used as it alters the brain amines [21]. After sacrificing, the brains were rapidly removed and concentrations of DA and 5-HT were measured by fluorimetry.

The brain was weighed and homogenized with 6 ml of cold acidified butanol at 800 x g. An aliquot from each homogenate served as a tissue sample. The internal standards were prepared by the addition of known amounts of standards (500µg each DA & 5-HT) to a portion of homogenate and processed in parallel with tissue samples. The reagent blanks and test samples for estimation were prepared following the same procedure described by Kari et al. [22] DA and 5-HT were read with an excitation and emission wavelength of 320/370 nm and 360/470 nm respectively with a slit width of 10/10 nm.

Statistical analysis

The data obtained from the performance on large open field was expressed as mean ± SEM and the results of each group were compared with negative control rats. The data obtained from frequency of stops and total duration of stopping at individual objects by different groups were categorized as More (includes sum of scores attained at two objects where rats have shown more frequency of stops and duration of time spent) and were compared with that of Less (includes sum of scores attained at two objects where rats have shown less frequency of stops and duration of time spent) using Bland-Altman analysis to determine the percentage difference and bias between the two categories at which rats have stopped and time spent. The data of number of visits to other objects on successive return to the same object by different groups was analyzed using one sample *t* test and are compared with the least number of visits for significance. One way ANOVA followed by Dunnet's *t* test was implied to report the effect of curcumin and paroxetine treatment on data obtained from water maze and monoamine levels of brain.

Results

Effect on frequency of stops at respective objects

Rats treated with peanut oil had shown only less discrimination in the frequency of stops at different objects. Bland-Altman analysis had shown a bias (difference in frequency of stops between two objects with more frequency and two objects with less frequency, expressed as bias ± SD) of about 27.56 ± 14.92, whereas quinpirole-treated rats had shown a marked discrimination in the frequency of stops at different locales (bias of 116.9 ± 11.09), showing that these rats have developed obsession toward two objects. Curcumin at a dose of 5 and 10 mg/kg had shown a bias of 46.07 ± 23.13 and 37.39 ± 15.1 respectively; the bias obtained with curcumin 10 mg/kg and paroxetine 26.54 ± 11.8 are comparable with that of control rats (Table 1).

Effect on total duration of stopping at respective objects

Quinpirole-treated rats developed obsessions (likeliness) toward two objects, and this can be understood by the increase in time spent at these objects; a bias of 181.91 ± 18.51 was observed. This is far more than the bias observed in control rats, i.e., 36.23 ± 37.41. Administration of curcumin 5 and 10 mg/kg had markedly reduced the difference shown between the objects to about 78.73 ± 37.66 and 61.83 ± 29.02 respectively and is comparable with that of paroxetine 58.07 ± 47.81 (Table 2).

Table 1 Effect of curcumin on frequency of stops at different objects

Group	Frequency of stops		Mean	% Diff.	Bias ± SD
	More	Less			
I	19.67 ± 1.55	15 ± 1.4	17.3	27.56	27.56 ± 14.92
II	12 ± 1.9	3.3 ± 0.71	7.6	116.9	116.9 ± 11.09
III	12.67 ± 2.3	8.5 ± 2	10.58	46.07	46.07 ± 23.13
IV	14 ± 2	9.6 ± 1.5	11.83	37.35	37.39 ± 15.1
V	14.3 ± 1.6	11.2 ± 0.6	12.6	26.5	26.54 ± 11.8

More and less denotes sum of two objects where rats have shown more or less frequency of stops respectively, SD = Standard deviation of bias.

Table 2 Effect of curcumin on duration of stopping at different objects

Group	Frequency of stops		Mean	% Diff.	Bias ± SD
	More	Less			
I	29.8 ± 3.2	21.5 ± 4.3	25.67	36.23	36.23 ± 37.41
II	41.49 ± 6.3	1.63 ± 0.61	21.78	181.9	181.91 ± 18.51
III	27.5 ± 3.61	11.75 ± 1.6	19.62	78.73	78.73 ± 37.66
IV	27.8 ± 7.12	14.07 ± 2.7	20.93	61.83	61.83 ± 29.02
V	25.5 ± 3.78	13.1 ± 1.32	19.25	58.07	58.07 ± 47.81

More and less denotes sum of two objects where rats have shown more or less frequency of stops respectively, SD = Standard deviation of bias.

Effect on number of visits to other objects in between returns to given object

The number of visits to other objects on successive visits decreased markedly for those objects where rats have developed obsessions. One sample *t* test analysis between the number of visits to other objects on successive return to each object (considered as B, C and D) with that of the object for which the number of visits to other objects is less (considered as object A) did not show any significant difference between visits to other objects in control rats (Object A – 2.83, B – 3.16, C – 3.5, D – 3.33). Whereas quinpirole treated rats have shown a significant difference for two objects (Object A–0.78,

B–1, C–3.67, D–4.23). Curcumin at 5 mg/kg did not show any deviation when compared with that of quinpirole-treated group, but curcumin at 10 mg/kg had increased the number of visits. A significant difference was observed for one object only (Object A – 3.16, B – 3.83, C – 5.33, D – 5.67) and is comparable with that of paroxetine (Object A – 3.5, B – 3.66, C – 4, D – 4.5) (Fig. 1).

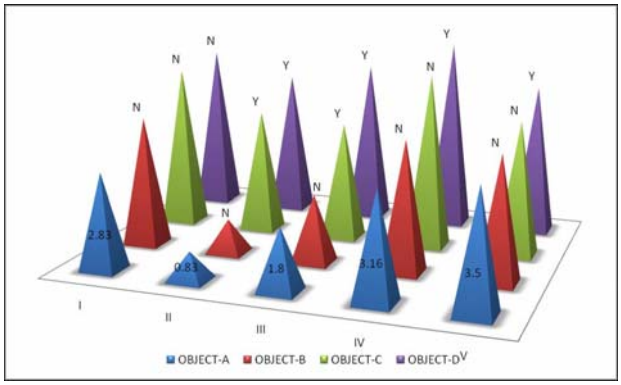

Fig 1 Number of visits to other objects on successive return to each object. N and Y indicate nonsignificant and significant differences, respectively, obtained by one sample t test comparision (n=6) of number of visits on successive return to the object with that of the object where less number of visits on successive return are shown.

Ritual-like behaviors

A characteristic ritualistic behavior, such as repeated grooming with hind paws and cleaning the snout with both forepaws, were exhibited by quinpirole-treated rats at those objects where obsessions have been developed. No such behaviors were observed in control rats, and the severity of these behaviors decreased markedly on treatment with curcumin and paroxetine.

Effect on spatial learning

Quinpirole treatment did not show any retrieval of the learned task (reaching the escape platform), but curcumin at a dose of 10 mg/kg had shown a good retention of memory and was significant than that observed with paroxetine (Fig. 2).

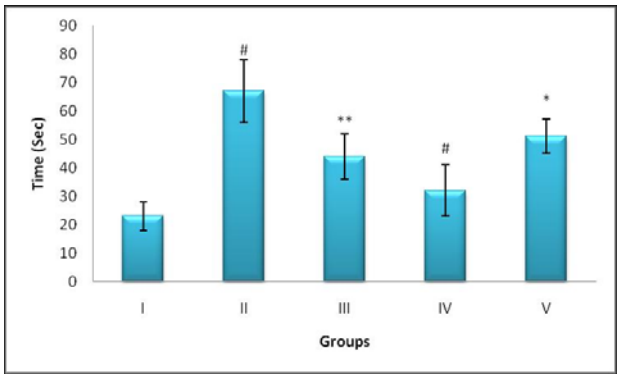

Fig 2 Effect on retention of learned task: the delay in time to reach the escape platform from the starting point on the last day of treatment after exploration on open field, each column represents mean ± SEM (n=6) of time taken by the rats to reach the escape platform from the starting point, Values of quinpirole treated are compared with that of control group, values of curcumin 5, 10 mg/kg and paroxetine treated were compared with that of quinpirole treated negative control rats. # p<0.001, ** p<0.01, * p<0.05.

Effect of curcumin on brain dopamine and serotonin levels.

A significant increase p<0.001 in the DA levels was observed in rats treated with quinpirole alone when compared with control. Rats treated with curcumin 5 and 10 mg/kg had shown a marked decrease in DA levels (p<0.01, p<0.001), but a marked increase in the serotonin levels was observed only at 10 mg/kg (p<0.05) when compared to that of negative control. Paroxetine treated rats had shown a significant increase in serotonin (p<0.05) with minimal effect on DA levels (Fig. 3).

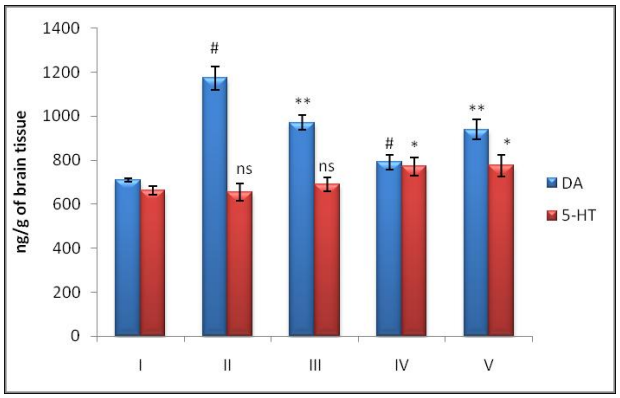

Fig 3 Dopamine and serotonin levels of whole brain: the effect of curcumin and paroxetine on dopamine and serotonin levels (nanogram/gram of wet tissue) in rat brain. Each column represents the mean ± SEM (n=6). Values of control, curcumin 5mg/kg, curcumin and paroxetine treated rats were compared with negative control. All the groups except control were treated with quinpirole. # p<0.001, ** p<0.01, * p<0.05, ns – non significant.

Discussion

Obsessive-compulsive disorder, resulting from the abnormality in signal processing by OFC, ACG and basal ganglia are currently treated with SSRIs and serotonin and norepinephrine reuptake inhibitors [23]. Apart from providing inadequate support, this is also involved in many adverse effects. The current study recommends a treatment that reduces the symptoms and progression of OCD along with memory disturbances. Though mechanisms underlying the pathogenesis of OCD are widely understood, there exists a controversy in suggesting the cause. As mentioned previously, one study suggests that the occurrence is due to excessive stimulation of OFC and ACG resulting in generation of excessive messages to basal ganglia [5], and another theory states that the damage to the OFC and ACG resulted in a loss of error detection abilities causing the brain to increase repetition of messages leading to OCD. The former was widely accepted because of its ability to explain various symptoms of OCD. This can be further substantiated by the present study that quinpirole, a D2/D3 agonist, is considered to increase the

dopaminergic activity to produce the symptoms.

SSRIs are widely used in the treatment of OCD, implying that serotonin is involved in its etiology. Dopaminergic over activity is also considered to be involved in OCD [24] as basal ganglia, the structure of the brain considered to be malfunctioning in OCD, is innervated with dopaminergic fibres. The caudate nucleus, a structure of basal ganglia that prevents the initial signal of "error" from the OFC to the thalamus does not function normally in those with OCD and therefore does not prevent this initial signal from recurring. This causes the thalamus to become hyperactive and creates a virtually never-ending loop of worry signals being sent back and forth between the OFC and the thalamus [25]. Hence, the OFC responds by increasing anxiety and engaging in compulsive behaviors in an attempt to relieve this apprehension. Memory disturbances are also associated with OCD [26], which can be due to abnormality in the dopamine levels of the hippocampus and amygdala, the two structures that actively participate in consolidation of recent and emotional memory, respectively [27]. Both these structures are widely innervated with dopaminergic fibres [28, 29] further confirming the involvement of dopamine in the etiology of memory disturbances in OCD.

The increased duration of stopping, frequency of visits and decreased number of visits to other objects on successive visits indicates the development of OCD symptoms. Performance of ritual-like movements at these objects can be exemplified as compulsions developed in OCD patient for obsessions. Treatment with curcumin had markedly reduced these observed changes, indicating its therapeutic potential in the treatment of OCD. Water maze exploration had shown memory impairment in quinpirole-treated rats and retrieval in curcumin-treated rats. The decrease in dopamine levels and increase in serotonin levels with curcumin treatment explains the therapeutic effect of curcumin. The predictive validity of this model can be explained based on the theory that a substantial interaction exists between the serotonergic and dopaminergic systems in two mid-brain regions, ventral tegmentum and substantia nigra, with dopamine-producing neurons being targets for serotonin cells. It has been explained that $5HT_{1A}$-auto-receptor activation inhibits dopamine release in the dorsal striatum of the mid brain and stimulates dopamine release in the nucleus accumbens [30]. This theory provides the key mechanism probably involved in the beneficial effect of SSRIs in the treatment of quinpirole-induced OCD, since quinpirole acts as an agonist on the D2 and D3 receptors in the striatal region of the mid-brain [16] thus increasing the dopamine levels. The increased serotonin concentration acts on $5HT_{1A}$-auto-receptors, inhibiting dopamine release. This can be further supported by a study that sertraline, an SSRI, has been reported to decrease the extracellular striatal levels of dopamine [31], and this decrease in dopamine levels, which is also exhibited by paroxetine in the present study, might have contributed to the protective effect of paroxetine in the treatment of qunipirole-induced OCD, providing a clue for the construct validity of the model.

Conclusion

Our results made it evident that curcumin exerts anti-OCD and memory- protective effects in a quinpirole-induced model of OCD. The mechanism involved in its anti-OCD effect might be due to accentuation of serotonin levels in various regions of the brain as observed in the present study and decrease in dopamine levels due to activation of 5HT1A-auto-receptors, thus contributing to the predictive and construct validity of the model [32]. However, further studies are essential to substantiate and validate the authenticity of these results in other models of OCD, which helps in investigating the role of curcumin to emerge as an effective counterpart in the treatment of OCD.

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