

Curcumin for Attention Deficit Hyperactivity Disorder: a Behavioral Preliminary Investigation

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Abstract

Background: Curcumin has protective actions in neuropsychiatric disorders. Its mechanism of action is associated with the restoration of catecholaminergic balance, reduction of oxidative/nitrosative stress, protection against inflammation, and neuroprotection. **Objective:** In a first approach, the study presents an empty review of the potential effect of curcumin on cognitive performance in attention deficit hyperactivity disorder (ADHD).

Methods: On a second moment, seeing the scarcity of studies and knowing that ADHD is related to hyperactive and anxious behavior, 20 spontaneously hypertensive Wistar rats (SHR) were divided into groups that received water (1 mg/kg/day), curcumin (50 mg/kg/day), or methylphenidate (1 mg/kg/day) for 42 days. Behavioral tests to assess activity (Open Field test), anxiety and impulsivity (Elevated Plus Maze, and Social Interaction), and memory (Y Maze and Object Recognition Test) were performed.

Results: Animals treated with curcumin showed less anxious and hyperactive behavior. Related to the memory, the results can be related to hyperactivity.

Conclusion: Thus, the data suggest that the treatments used here can beneficially modulate the anxious and hyperactive behavior of SHR.

Highlights

- There is an empty review relating curcumin ADHD;
- SHR treated with curcumin showed less anxiety;
- Curcumin decreased the hyperactive behavior in SHR.

1. Introduction

Neurodevelopmental disorders affect the functioning of the central nervous system in the motor, cognitive, communication, and behavior domains during the developmental period, being subject to changes in neural maturation (Thapar et al., 2017). Despite appearing in childhood, before puberty, these disorders can remain throughout adult life (Moffitt et al., 2015). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013), attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder are examples of these disorders.

Individuals suffering from ADHD exhibit hyperactivity, inattention, impulsivity, and problems in social interaction (Sharma, Couture, 2014). Although abnormalities in several brain regions and disturbances of the catecholaminergic pathway have been demonstrated, the pathophysiology of ADHD is not completely understood, but as a multifactorial disorder, has been associated with an increase in oxidative stress and neuroinflammation (Corona et al., 2020). Currently, the pharmacological treatment used for ADHD seeks to improve attention, reducing distraction and impulsive behavior by increasing the levels of catecholamines in the brain (Briars, Todd, 2016). Methylphenidate (MPH) is the most frequently used

drug for the treatment of ADHD, it acts by the increase of extracellular dopamine (DOPA) and norepinephrine (NE) (Storebo et al., 2018). However, its use has been associated with side effects, including loss of appetite, dry mouth and eyes, anxiety, nausea, insomnia, hyperhidrosis, restlessness, dyskinesia, and dizziness (Wenthur, 2016). In this sense, the search for alternative treatments for ADHD has increased, including natural compounds (Searight et al., 2012; Jaeschke et al., 2021).

Curcumin is a polyphenol derived from the rhizomes of *Curcuma longa* Linn (Zingiberaceae) (Kocaadam, Sanler, 2017) with potential neuroprotective effects, acting on neurological and psychological disorders, due to its ability to cross the blood-brain barrier and its anti-inflammatory and antioxidant effects (Mishra, Palanivelu, 2008; Wang et al., 2010; Ulamek-Kozioł et al., 2020; Zhong et al., 2020). Besides, curcumin is able to influence levels of serotonin, DOPA, NE, and glutamate in the CNS (Lopresti et al., 2012).

Considering the action of curcumin in some biological pathways that may be of potential interest in the treatment of ADHD, this study reviewed the potential effect of curcumin on cognitive performance in children with ADHD and animal models. This review was done in the databases PubMed, EMBASE, ScieLO, Cochrane Central Register of Control Trials (CENTRAL), and Web of Science. Searches were also carried out in gray literature libraries such as OpenGray, GreyLit e GreyNet. The complete search strategy can be found in Supplementary Material. A total of three studies met all inclusion criteria and were selected for review, but they were clinical trial protocols that were discontinued (Figure 1S). The preliminary characteristics of the three clinical trials are shown in Table 1S. These studies proposed to verify the effectiveness of curcumin in children and adolescents of both genders diagnosed with ADHD. Curcumin was administered in capsule or candy form, with a dose ranging from 80 mg to 500 mg twice a day. According to the registration and contact with the authors, studies 2 and 3 (See Table 1S) were discontinued due to how curcumin was administered, reflecting problems in swallowing and palatability (personal communication).

Therefore, the current study aimed to preliminarily investigate whether treatment with curcumin would alter behavioral patterns in spontaneously hypertensive rats (SHR).

2. Methods

2.1. Animals

The study was conducted with fifteen male Wistar (SHR) rats and 5 Wistar Kyoto (KY), obtained from the vivarium of the Experimental Cardiology Center of the Institute of Cardiology (Porto Alegre-RS) with 7 weeks of age, weighing between 180 g and 200 g. The animal care and experimental procedures were strictly conducted in accordance with the Guide for Laboratory Animal Care in Research Experiments of the National Council for Animal Experimentation Control (CONCEA) and accordance with the ARRIVE Guidelines (Kilkenny et al., 2010). They were also approved by the Institutional Committee for Animal Care and Use from ULBRA under Protocol n° 2019.567. Five (5) rats per box were maintained with food and water ad libitum in a temperature-controlled room ($25 \pm 2^\circ\text{C}$), while under a 12-h light/dark cycle.

2.2. Experimental design

Treatments were administered for 42 days via gavage (p.o.) daily. Curcumin (Infinity Pharma, São Paulo, Campinas, Brazil) was suspended in 0.5% carboxymethylcellulose (Pharmacia Amphora, Belo Horizonte, Minas Gerais, Brazil) and was then diluted in water immediately before use. Treatments consisted of administration of curcumin 50 mg/kg (SHR-C) (Marques et al., 2021), or vehicle (1 mL/kg) (SHR-V), or methylphenidate (1 mg/kg) (Kim et al., 2011). KY animals received vehicle only (1mL/kg). All groups were submitted to behavioral tests and after performing these tests, the animals were euthanized by isoflurane overdose (Figure 1).

2.3. Behavioral tests

2.3.1. Open Field

The arena consisted of an acrylic square measuring 60 cm in diameter and 50 cm in height, subdivided into 16 concentric sections. The animals were placed individually in the center of the device and observed for 5 min. For the observations, the frequencies of locomotion (crossings) and raising of the animals (rearings) were computed (Broadhurst, 1960).

2.3.2. Elevated Plus Maze

The elevated plus-maze test was used to measure anxiety-related behaviors according to Pellow et al. (1985). The apparatus consists of a cross-shaped apparatus raised 50 cm above the ground, with four arms of 50 x 10 cm each, two open and the other two perpendiculars to them, closed with 40 cm acrylic side walls tall. The animals were individually exposed in the center with the nostril directed towards one of the closed arms and observed for 5 min. The frequencies of entries into the closed and open arms and the time spent in the closed and open arms were computed. Exploratory activities were computed as dippings (when the animal sticking its head outside of the maze border and toward the floor).

2.3.3. Y Maze

The device, made of black wood, has three equal arms (50 x 10 x 20 cm, each arm) 120° apart and was placed in a room with visual cues on the walls to facilitate the spatial location of the animals. The protocol consisted of two sessions separated by an interval of 1 h. In the first session, the animal was placed at the end of one of the arms, called the main arm, and had free access to explore the other arm for 5 min. The third arm was blocked by a guillotine door and was called the new arm. The rat was then removed from the maze and returned to the housing box. After 1 h, in the second session, the animal was again placed in the main arm of the maze to freely explore all three arms for 5 min. The number of entries and length of staying for each arm were recorded (Dellu et al., 1992).

2.3.4. Object Recognition

The test was carried out in the open field arena where on day 1 the rat was placed in the open field and the presence of two identical objects for free exploration for 5 min. After 90 min the rat was placed again,

but one of the familiar objects was replaced by a new (unfamiliar) object, allowing free access to the objects for 5 min. After 24 hours a third object replaced the new object. The exploration of the objects was evaluated through the investigative behavior of the rat (smelling or touching the objects with the front paws or nose and biting the objects) (Lueptow, 2017). From these data, the preference index was calculated: $(T_{\text{novel}} \times 100) / (T_{\text{novel}} + T_{\text{familiar}})$, where T_{novel} was the time spent exploring the displaced object, and T_{familiar} was the time spent exploring the non-displaced object.

2.3.5. Social Interaction

The test was performed in the open field arena. Pairs of unknown SHR rats were placed simultaneously in the apparatus approximately 30 cm apart. Social behavior and motor activity parameters were evaluated for 10 min. Time spent in active (sniffing and following) or passive (when animals maintain a skin-to-skin distance of 5 cm) was scored for each rat. The total SI time was quantified for each rat through the sum of the time spent involved in active and passive activities in a bright and familiar environment (moderate anxiety) (Gogas et al. al., 2007).

2.4. Statistical Analysis

Data were expressed as mean \pm SEM and evaluated using the Graphpad Prism V statistical program (GraphPad Software, California, USA). The behavioral data were tested for normality through the Kolmogorov-Smirnov test and assessed using One-way analysis of variance (ANOVA One-way) followed by Student-Newman-Keuls (SNK) test as post hoc. In the social interaction test, a one-tailed unpaired T-test was used. In the analyses, confidence intervals of 95% and significance levels of 5% ($p < 0.05$) were considered.

3. Results

3.2. Animal Behavioral assessment

3.2.1. Open Field

In the evaluation of crossings, the KYT-V group (25.40 ± 2.09) moved less than the SHR-V (51.60 ± 3.50 , $p < 0.001$) and SHR-M (36.8 ± 2.20 , $p < 0.05$) groups. The SHR-C group (26.0 ± 2.83) showed locomotion similar to the KYT-V group, and significantly lower when compared to the SHR-V ($p < 0.001$) and SHR-M ($p < 0.05$) group (Figure 2a).

Regarding rearings, the KYT-W group presented a lower exploratory behavior (5.80 ± 1.74 , $p < 0.001$) when compared to the other groups (Figure 2b). However, SHR-C (21.0 ± 2.83 , $p < 0.01$) explored the environment less than SHR-V (51.6 ± 3.50).

3.2.2. Elevated Plus Maze

The KYT-V group remained longer in the closed arm (281.80 ± 11.15 s) and less in the open arm (19.80 ± 11.14 s), although there was no difference between the groups (Figure 3a). SHR-M entered the open arm

more times (4.40 ± 1.03) and remained longer (76.6 ± 22.45) than the others, but also without significant difference (Figure 3b). In the analysis of the exploratory behavior (dippings) no significant differences were identified between the groups, however, the SHR-C group (6.80 ± 1.03) showed similar values to the KYT-W group (5.80 ± 0.91) (Figure 3c).

3.2.3. Y Maze test

In the assessment of spatial memory, it is possible to observe that the SHR-V group (5.00 ± 0.45 , $p < 0.001$) entered the new arm more often compared to the KYT-V group (1.20 ± 0.48) and the SHR-M group (1.20 ± 0.48) (Figure 4a). The SHR-C group (3.6 ± 0.51 , $p < 0.05$) entered less often compared to the KYT-C and SHR-M groups. Related to time in the new arm, the same pattern of behavior can be observed, where KYT-V (20.00 ± 8.35 s) and SHR-M (48.6 ± 18.91 s) remained for less time when compared to SHR-C (100.2 ± 8.31 , $p < 0.01$ and $p < 0.05$ respectively) and SHR-V (127.8 ± 13.44 s, $p < 0.001$ and $p < 0.01$ respectively) (Figure 4b).

3.2.4. Object Recognition

There were no significant differences in short-term memory between the animals of the different groups ($p = 0.52$) (Figure 5a). However, in long-term memory, the preference index of SHR-M animals ($94.57 \pm 3.37\%$) showed significant differences when compared to KYT-A ($71.67 \pm 3.33\%$) and SHR-C (70.38 ± 7.50) animals ($p < 0.05$) (Figure 5b).

3.2.5. Social Interaction Test

Regarding passive interactions between the SHR-V and SHR-C groups, no significant difference was found in time ($p = 0.29$). However, SHR-C was more active (9.25 ± 1.51 s, $p < 0.05$) than SHR-V animals (5.5 ± 1.30 s).

4. Discussion

Hyperactivity and inattention may be related to the insufficient function of the catecholamine (i.e., DOPA and NE) system in the brain. According to Cai et al., (2021), ADHD symptoms are associated with decreased synaptic DOPA and NE concentrations. In addition, there is a dysfunction of information transmission between inhibitory synapses and excitatory synapses (Xi, Wu et al., 2021), where occurs an atypical balance of neural excitation and inhibition (E/I) being GABA and glutamate as contributing (Mamiya et al., 2021). Although ADHD is associated with dysregulation of the catecholaminergic pathway and E/I balance in the brain, data also point to the contribution of oxidative stress and neuroinflammation in the pathophysiology of ADHD (Prince, 2008; Lopresti, 2015; Leffa et al., 2017; Darwish et al., 2019; Dursun et al., 2021).

SHR animals are used as ADHD models because they demonstrate hyperactive behavior even in familiar environments (Langen, Dost, 2011), anxiety (Ji et al., 2014), and spatial learning memory deficit (Kim et al., 2011). Disturbances in the functions of the neurotransmitters glutamate, DOPA, and NE in the brain of SHR and information obtained from patients with ADHD suggest a defect in neuronal circuits that are

required for reward-oriented associative learning and memory formation (Russel, 2003). Sagvolden et al. (2005) suggest that the altered function of DOPA fails to adequately modulate the glutamatergic excitatory and GABAergic inhibitory signal transmission. Thus, persistent hypertension in SHR rats has depressive effects on glutamatergic and GABAergic parameters of the synaptic activity of neurons, which would influence the animals' learning and memory (Russel, 2003). The hypodopaminergic theory of ADHD states that hyperactive and inattentive behaviors are caused by low levels of DOPA, which leads to NMDA (N-methyl-D-aspartate) and AMPA (α -amino-3-hydroxy-5-methyl- receptors). 4-isoxazole propionic) become more active, resulting in increased glutamatergic production. In this situation, glutamate would normally release more DOPA, however, in the brain of individuals with ADHD, this feedback does not appear to occur (Miller et al., 2013). Furthermore, it is worth noting that the release of DOPA stimulated by glutamate in the nervous system of SHR is greater (Warton et al., 2009).

Furthermore, norepinephrine activity influences the acquisition and reinforcement of conditioned responses, and catecholamine-glutamate interactions strengthen and change the reinforced and adaptive behavior (Mingote et al, 2004). Therefore, the basic treatment for ADHD is stimulant drugs, eg, methylphenidate, which increases synaptic DOPA by directly blocking the DOPA transporter (DAT) (Biederman et al., 2004) or atomoxetine, which increases extracellular levels of noradrenaline (Arnsten, 2010). Also related to noradrenaline, in SHR, the inhibition of NE release mediated by the AMPA receptor, which is necessary for the NMDA effect, is impaired and glutamate stimulation of NE release is greater than that of Wistar Kyoto and Sprague rats –Dawley rats, in the prefrontal cortex and hippocampus (Howells, Russell, 2008).

The evaluation of several natural products has been carried out in search of possible therapies for ADHD. Thus, knowing that curcumin acts on several biological pathways including oxidative/nitrosative, and inflammatory (Wang et al., 2010; Bhandari, 2015; Tsuda, 2018; Pan et al., 2019), its protective actions are reported in several neurodegenerative and neuropsychiatric disorders (Mythri, Bharath, 2012). This compound can increase the inhibition of DOPA and NE reuptake by different pathways (Tabeshpour, et al., 2019), acting on neurotransmitter imbalances implicated in bipolar disorder (Anderson, Maes, 2015), anxiety disorders (Furtado, Katzman, 2015), schizophrenia (Davis et al., 2014) and autism (Rossignol, Frye, 2014).

Thus, the present study was designed by the fact that curcumin (30 mg/kg, p.o.) demonstrated neuroprotective action in diseases involving catecholaminergic deficits, mainly dopaminergic and noradrenergic deficits (Tamegart et al., 2019). Motawi et al. (2020) demonstrated that curcumin (80 mg/kg/day, p.o.) can significantly increase noradrenaline levels in the brain of rotenone-induced Parkinson's disease rats. In the same model, Madiha, Haider (2019) found that curcumin (100 mg/kg p.o.) for 2 weeks improved neurotransmitter levels as compared to rotenone injected rats. In a depression model induced by reserpine, curcumin-coated iron oxide nanoparticles for two weeks elevated serotonin (5-HT), NE, and DA levels (Khadrawy et al., 2021). Saied et al. (2020) demonstrated the same result, where curcumin (100 mg/kg, p.o., daily for one month) improved DOPA and NE levels in striatum and hippocampus in ovariectomized rats. They also showed that the treatment resulted in the down-

regulation of monoamine oxidase b and up-regulation of tyrosine hydroxylase, as well as the DOPA receptor mRNA in the limbic region. In addition, inflammatory and oxidative parameters were ameliorated in the limbic system.

In this study, animals SHR treated with vehicle (SHR-V, negative control) moved around and further explored the open field arena. On the other hand, SHR animals treated with curcumin (SHR-C, 50 mg/kg/day, p.o.) for 42 days tended to demonstrate less anxious and hyperactive behavior, identified by the number of crossings in the open field test and active behavior in the social interaction test. Methylphenidate-treated animals also showed differences in locomotor but not exploratory behavior compared to SHR-V. Although anxious behavior measured by the EPM was not modulated by any treatment, Kishikawa et al., (2014) state that this test also reflects SHR's impulsiveness in search of novelties, which we can also suggest was unchanged. In the social interaction test, curcumin significantly showed more active behavior. In this test, environmental manipulations (lighting and familiar or unfamiliar arena) can increase or decrease the number of times rats interact, thus allowing the assessment of anxiolytic (increased interaction) or anxiogenic (decreased interaction) effects (Gogas et al. al., 2007). In this sense, the anxiolytic activity of curcumin has already been determined in several studies (Ceremuga et al., 2017; Lee, Lee, 2018; Marques et al., 2021).

In a recent systematic review, Sanei and Saberi-Demneh (2019) revealed that curcumin moderated or reversed the memory deficit in animal models in rodents, not being considered a placebo effect. However, the results of the Y-maze tests in our study demonstrate significant differences where SHR-C animals entered more and spent more time exploring the new arm of the apparatus when compared to SHR-M and KYT-V animals. However, in the object recognition test, only SHR-M affected long-term memory. Thus, the results are in line with those of Guo et al. (2012), where chronic methylphenidate administration did not affect the spatial learning performance of SHR animals during Morris water maze training, but significantly improved memory. According to the systematic review by Leffa et al. (2019), methylphenidate increases attentional and mnemonic performance in SHR animals. However, the drug does not reduce hyperactivity in SHR at low and medium doses. It should be noted here that according to Sontag et al. (2013), data on spatial working memory deficits in SHRs are not consistent, as they may be related to locomotor activity. Furthermore, the authors also mention that compared to KY rats, SHRs did not show any impairment in spatial working memory and reference memory. When the locomotor activity of rats was taken into account, the working memory and reference memory of SHRs were significantly better than in KY rats, according to the authors.

Many studies are carried out concerning the neuroprotective aspects of curcumin, especially in neurodegenerative diseases. However, related to ADHD, no study was developed and completed. It should be noted that this review was restricted to Portuguese and English, therefore studies in other languages may have been ignored in the selection of papers. Although we have not found any preclinical or published clinical studies linking ADHD with curcumin, this review suggests that studies should be continued to clarify the possible use of curcumin as a therapeutic agent.

Based on the above, the available literature on the effects of curcumin in SHR animals with a focus on neural aspects remains empty. Therefore, through the results of the present study, it can be suggested that this non-pharmacological approach could lead to beneficial effects on behavior in SHR. However, it is worth noting that there is a limitation of the low statistical power of the sample size. Therefore, studies should be conducted in order to assess the time and dose-dependent effect of curcumin treatment and its association with longer exercise protocols in SHR animals. Higher concentrations of curcumin could be needed to produce a more pronounced effect given its low oral bioavailability (Lopresti, 2018). However, in this study, the oral route was chosen as it is the most routine route of administration in clinical practice. Although with limitations, the findings suggest that the protocols used in this study are of great value to modulate the behavior of these animals, but further investigations are needed.

Declarations

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Author Contribution: The authors declare that all data were generated in-house and that no paper mill was used. All authors read and approved the manuscript and all of them have contributed equally.

Ethics Approval: The animal care and experimental procedures were strictly conducted in accordance with the Guide for Laboratory Animal Care in Research Experiments of the National Council for Animal Experimentation Control (CONCEA) and accordance with the ARRIVE Guidelines. They were also approved by the Institutional Committee for Animal Care and Use from ULBRA under Protocol nº 2019.567.

Data availability: All data generated or analyzed during this study are included in this published article [and its supplementary information files.

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Figures

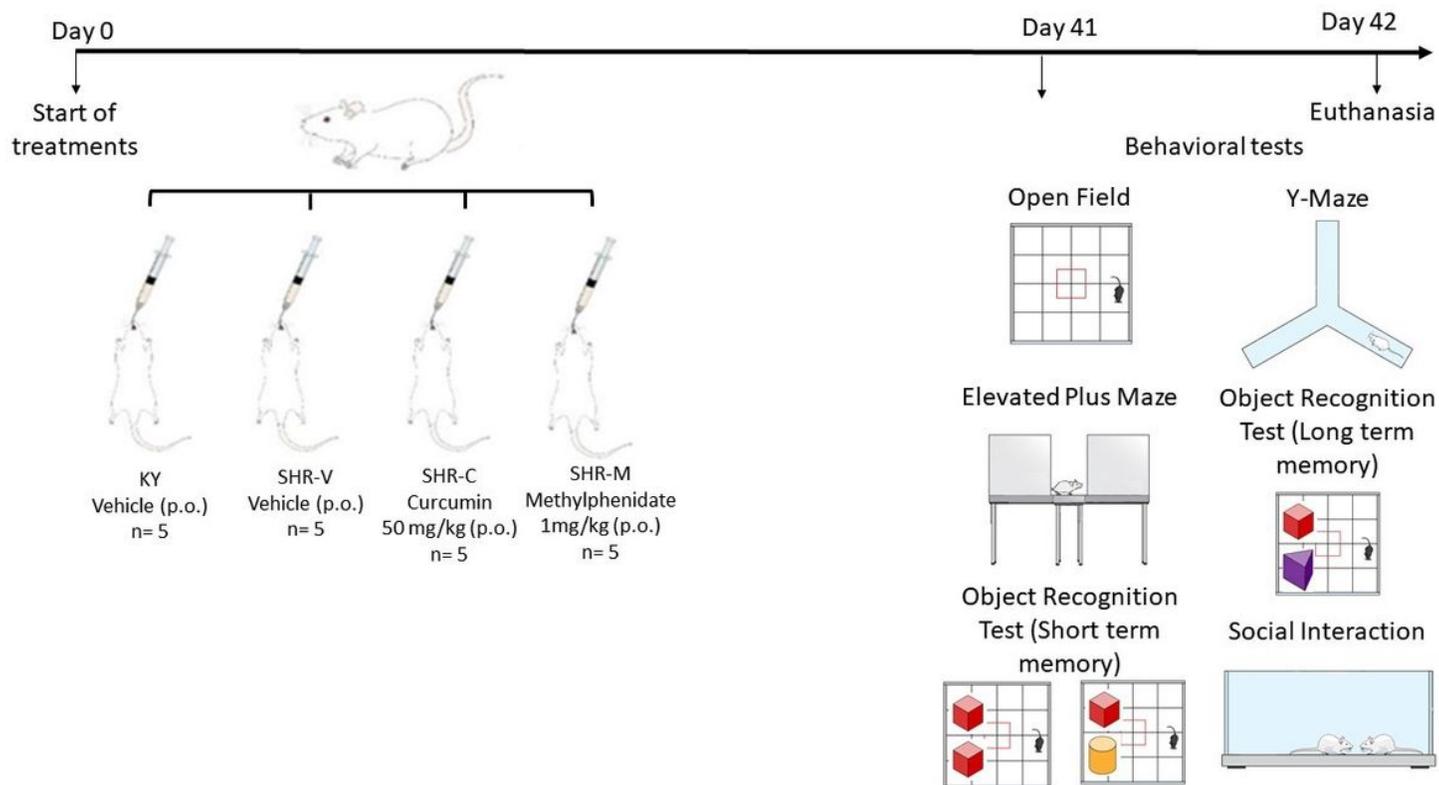


Figure 1

Experimental protocol used in the study. Euthanasia was conducted after the behavioral tests.

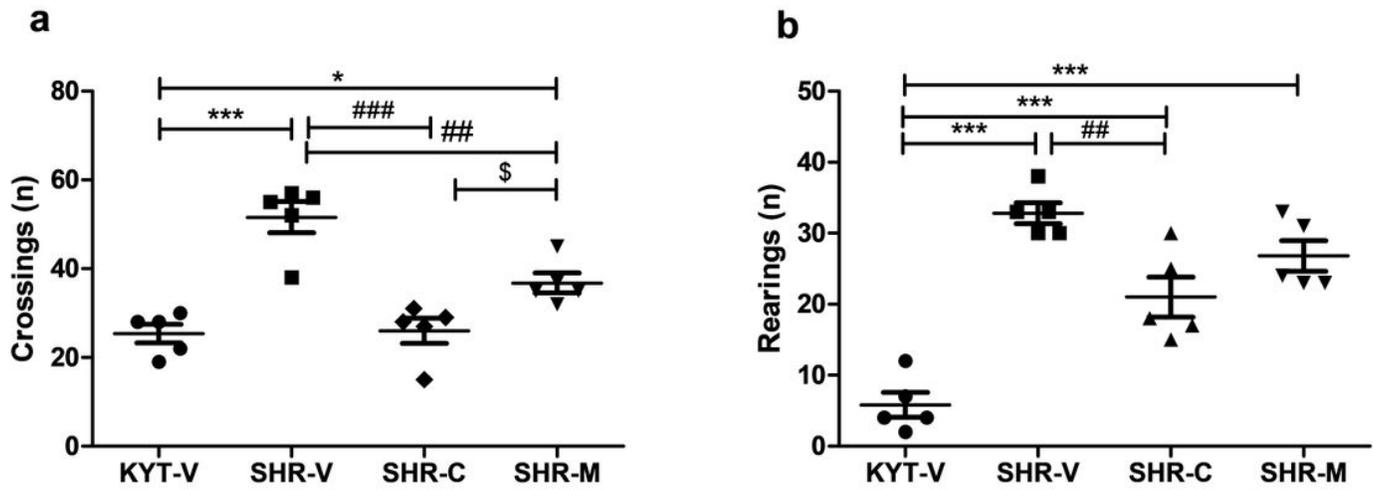


Figure 2

Effect of curcumin on locomotor (a) and exploratory (b) activity in the open field test. Data represent mean and standard error (n=5 animals per group). KYT-V: Kyoto animals treated with vehicle (p.o.); SHR-V: vehicle p.o.); SHR-C: curcumin (50 mg/kg, p.o.); SHR-M: methylphenidate (1 mg/kg, p.o.), for 42 days. **p<0.01, ***p<0.001 when compared to the KYT-A group. ##p<0.01, ###p<0.001 when compared to SHR-V. \$p<0.05 when compared to the SHR-C group. ANOVA One-way following SNK post hoc.

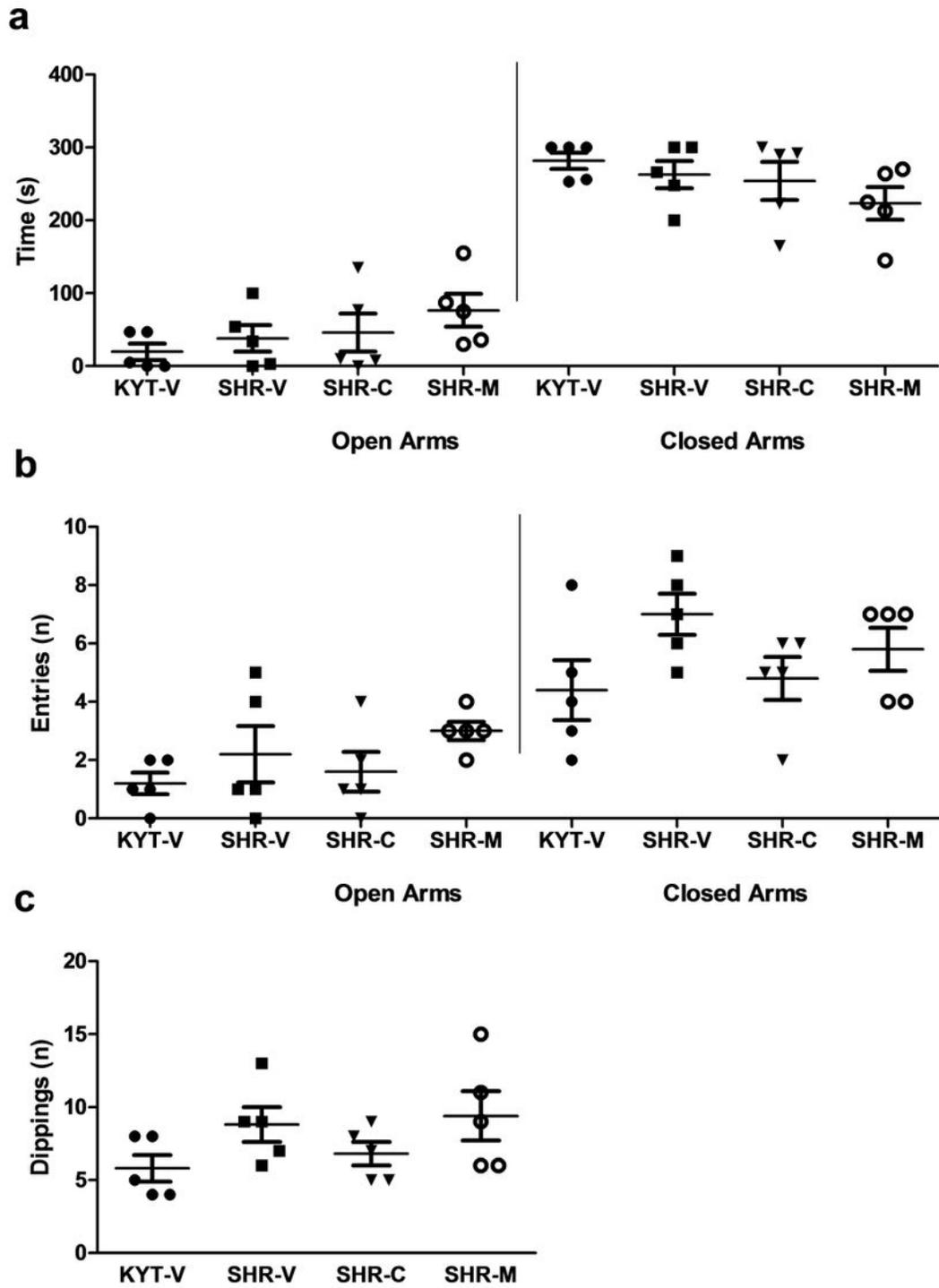


Figure 3

Effect of curcumin on anxious behavior assessed by Elevated Plus Maze time-spent (a), entries (b), and dippings (c). Data represent mean and standard error (n=5 animals per group). KYT-V: Kyoto vehicle (p.o.); SHR-V: vehicle (p.o.); SHR-C: curcumin (50 mg/kg, p.o.); SHR-M: methylphenidate (1 mg/kg, p.o.), for 42 days. ANOVA One-way following SNK post hoc.

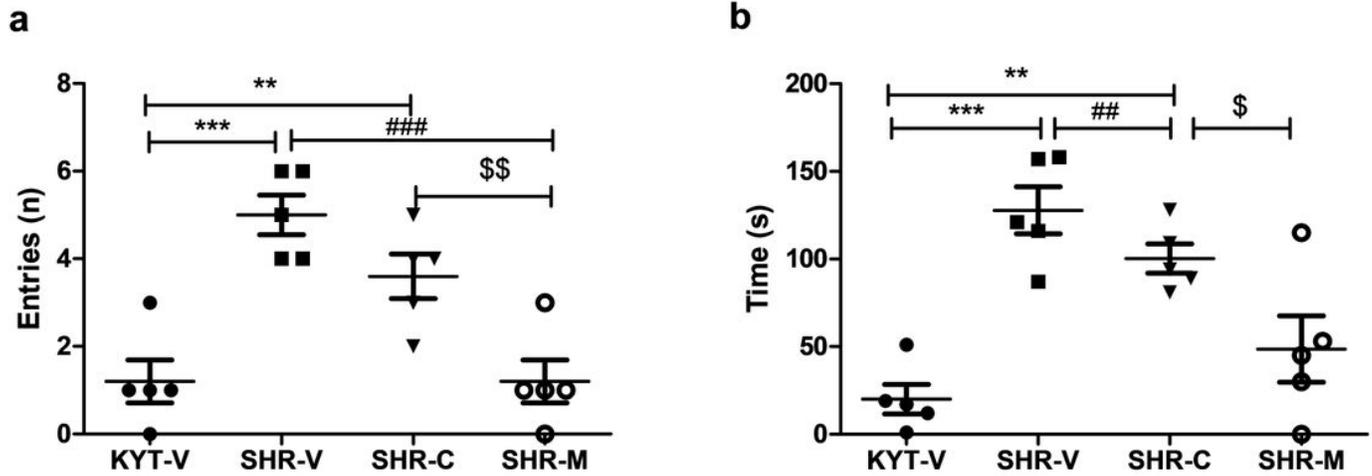


Figure 4

Effect of curcumin on spatial memory assessed by Y-maze related to entries (a) and time-spent (b) in the new arm. Data represent mean and standard error (n=5 animals per group). KYT-V: Kyoto animals treated with vehicle (p.o.); SHR-V: vehicle p.o.); SHR-C: curcumin (50 mg/kg, p.o.); SHR-M: methylphenidate (1 mg/kg, p.o.), for 42 days. **p<0.01, ***p<0.001 when compared to the KYT-A group. #p<0.05 and ##p<0.01 when compared to SHR-V. \$ p<0.05, \$\$ p<0.01 when compared to the SHR-C group. ANOVA One-way following SNK post hoc.

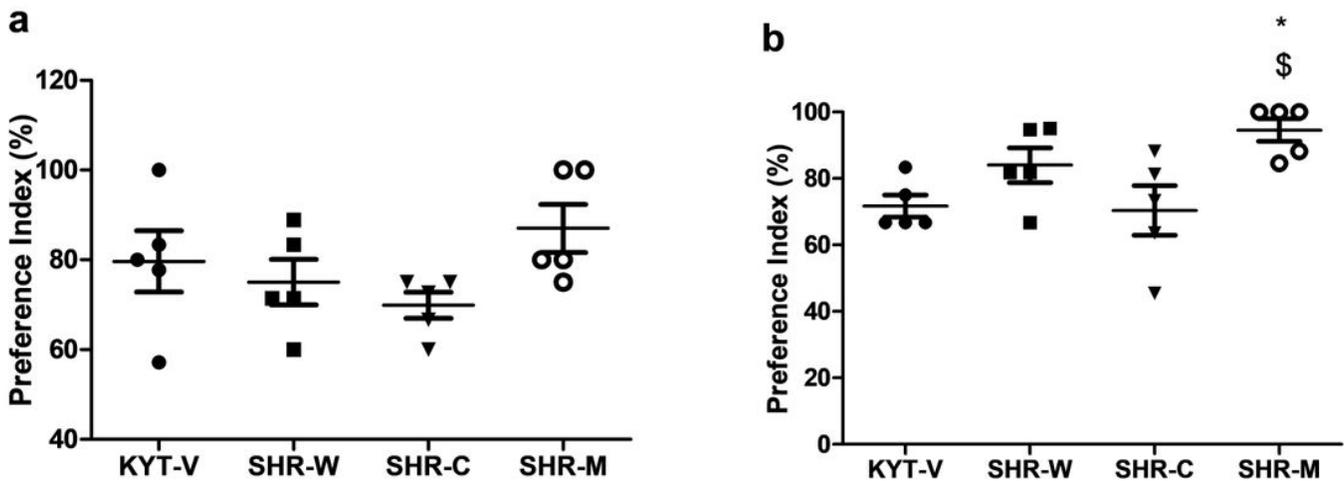


Figure 5

Effect of curcumin on short-term (a) and long-term (b) memory assessed by Object Recognition test. Data represent mean and standard error (n=5 animals per group). KYT-V: Kyoto animals treated with vehicle (p.o.); SHR-V: vehicle p.o.); SHR-C: curcumin (50 mg/kg, p.o.); SHR-M: methylphenidate (1 mg/kg, p.o.), for 42 days. *p<0.05 when compared to the KYT-A group. \$ p<0.05 when compared to the SHR-C group. ANOVA One-way following SNK post hoc.

Supplementary Files

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