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Original Article

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Protective Effects of Curcumin and Sertraline on the Behavioral Changes in Chronic Variable Stress-Induced Rats

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Behavioral characteristics of the animal models and humans are impaired in chronic stress. The present study aimed to evaluate and compare the protective effects of sertraline and curcumin on stress-induced learning and memory impairment, anxiety and anhedonia in rats. Male rats were divided into seven groups: stress+water, stress+olive oil, stress+curcumin (100 mg/kg/day), stress+sertraline (10 mg/kg/day), curcumin, sertraline, and control groups. The rats were exposed to chronic variable stress for 56 days. At the end of 40 days and while the previous treatments were continued, the rats were tested in the eight radial maze, elevated plus maze, and sucrose consumption for learning and memory, anxiety, and anhedonia, respectively. In comparison to the non-stressed group, stress+water and stress+olive oil groups revealed a significantly lower percent of correct choices and higher reference and working memory errors during learning and retention phases ($p<0.001$). In addition these stress groups showed a significant lower percent of the open arms time and open arms entries in the elevated plus maze and consuming less sucrose solution. In addition, the stress+curcumin and stress+sertraline groups showed a better performance in the evaluated parameters of the radial arm maze, elevated plus maze, and sucrose consumption tests. It appears that curcumin and sertraline have the similar effectiveness on behavioral changes in chronic variable stress-induced rats.

Key words: curcumin, sertraline, memory deficits, anxiety, stress, rat

INTRODUCTION

Chronic stress affects structure, physiology, and behavior [1]. A variety of studies have also shown an increased risk for memory deficit and changes in learning by chronic stress [2]. Stressful events of life also play a role in the etiology of depression and anxiety [3, 4]. When a chronic and permanent stimulation caused by stress exceeds the body capacity to maintain homeostasis, it can result in psychopathological sequels, including depression and anxiety [5]. Normal structure and function of the brain are altered by severe and/or chronic stress [6]. A variety of changes, including neuronal excitability, neurochemistry, and structural as well as functional plasticity of some brain areas, such as medial prefrontal cortex and hippocampus are adversely affected during stress [6]. Learning and memory impairing was reported after chronic stress in both animal models and human beings [7-11]. It has been

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shown that Chronic Variable Stress induces depression, anhedonia, and emotional reactions, such as anxiety and fear, in animal models [12-14]. A variety of chemical compounds including natural and synthetic substances have been used to ameliorate or prevent the effect of stress on the behavioral changes in animals and humans [9, 15-17]. The present study also aims to evaluate and compare the effects of a natural and a synthetic substance; i.e., curcumin and sertraline, on the stress-induced behavioral changes in an animal model.

Curcumin is the principal curcuminoid of the popular Indian spice turmeric. It is the main component of curcuma longa and has been used in the Indian and Chinese systems of medicines. It has been used for its diverse biological actions, such as antioxidant, anti-inflammatory, anticarcinogenic, antimicrobial, and neuroprotective effects [16-22]. Curcumin has also reported to have protective effects in animal models of diseases, such as Alzheimers, parkinsons, and epilepsy [23, 24]. More recently, researchers have reported that the individuals consuming curcumin in daily life have sharper brain function and higher cognitive abilities [23, 24]. In another study, curcumin was shown to protect the dopamine producing cells of the substantia nigra area of the brain in a rat model of Parkinson's disease [16, 17]. Selective serotonin reuptake inhibitors (SSRIs) are the primary medications prescribed owing to their effectiveness as well as relatively mild side effects and because they are less toxic in overdose compared to other antidepressants. Sertraline is primarily used to treat major depression in adult patients [25]. Its neuroprotective and antioxidant action have also been reported in neurodegenerative diseases [10, 26]. Besides, various reports have suggested the beneficial effect of sertraline in animal model depression [27-29].

The aim of the present study was to evaluate and compare the possible protective effects of sertraline and curcumin on the stress-induced learning and memory impairment, anxiety and anhedonia. A rodent model of chronic variable stress was proposed and learning and memory were examined using radial arm maze. Moreover, anxiety in the rats is tested using elevated plus maze [30]. Anhedonia is tested as the rodent consumption of sucrose appears [31].

MATERIALS AND METHODS

Animals

Eighty-four adult male Sprague-Dawley rats (260±20 g) were obtained from the laboratory animal's center of Shiraz University of Medical Sciences, Shiraz, Iran. The Ethics Committee of the University approved the animal experiment (Approval No: 91-6124). The male rats were randomly assigned to experimental and control groups. Each group included 12 rats that were housed under standard conditions, room temperature (22~24°C), and a 12:12 h light-dark schedule and had free access to water and food.

The animals were divided into seven groups each containing 12 rats: (I) stress +water group daily receiving stress and distilled water, (II) stress +olive oil group daily receiving stress and olive oil, (III) stress+curcumin group daily receiving stress and curcumin (100 mg/kg/day) solved in olive oil [22, 32-34], (IV) stress+sertraline group daily receiving stress and sertraline (10 mg/kg/day) solved in distilled water [35], (V) control group, (VI) curcumin group receiving curcumin (100 mg/kg/day) solved in olive oil [22, 32-34], and (VII) sertraline group receiving sertraline (10 mg/kg/day) solved in distilled water [35]. All the animals were treated by gavages every day for 8 weeks.

Dose of curcumin was determined according to our previous study. It showed 100 mg/kg/day as the appropriate dose of curcumin with no side effects on the liver, kidney, and blood levels of aspartate aminotransferase, alanine aminotransferase, urea nitrogen, and creatinine [21, 32-34]. Dose of sertraline was selected according to the previous studies [25]. Since it is chronically used in our practice, this period and dosage has been accepted as the period of usage for displaying its chronically effects [35].

Stress model

The 84 study animals were randomly divided into seven groups (n=12). The animals were submitted to a chronic variable stress regime over a 56-day period or remained in their home cages without stress manipulation [36]. The chronic variable stress is described in Table 1. The schedule of the different manipulation exerted on the animals subjected to the stress and treatments are presented in Table 2.

Behavioral tests

All the behavioral tests were performed in an experimental room, constant noise, and temperature controlled environment. It should be noted that the animals were allowed to adapt to the experimental room. It should be mentioned that the individual who was responsible for performing the assessment was blind to the experimental conditions of each animal. 84 rats in seven groups (n=12) were tested for anxiety and anhedonia and 70 male rats (n=10) were subjected to the memory and learning tests.

Assessment of task in the eight arm radial maze

Working memory can be explained as a memory for an object, stimulus, or location that is used within the evaluation session, but not typically between the sessions [5]. Reference memory

Table 1. The protocol for induction of the chronic variable stress (CVS) in 56 days for the rat model

Day	Stressor applied
1	Cold restraint (1.5 h)
2	Inclination of home cages (4 h)
3	Flashing light (2 h)
4	Restraint (2 h)
5	Isolation
6	Isolation
7	Isolation
8	Damp bedding (2 h)
9	Inclination of home cages (6 h)
10	No stressor applied
11	Flashing light (2 h)
12	Water deprivation (24 h)
13	Restraint (3 h)
14	Damp bedding (3 h)
15	Inclination of home cages (4 h)
16	Cold restraint (2 h)
17	Flashing light (3 h)
18	Restraint (2.5 h)
19	Damp bedding (3 h)
20	Isolation
21	Isolation
22	Isolation
23	Cold restraint (1.5 h)
24	Water deprivation (24 h)
25	Inclination of home cages (4 h)
26	Restraint (3 h)
27	Flashing light (3 h)
28	Restraint (1 h)
29	Damp bedding (2 h)
30	No stressor applied
31	Water deprivation (24 h)
32	Inclination of home cages (6 h)
33	Flashing light (2 h)
34	Cold restraint (2 h)
35	Isolation
36	Isolation
37	Isolation
38	Flashing light (3 h)
39	Damp bedding (2 h)
40	Restraint (3 h)
41	Cold restraint (1.5 h)
42	Inclination of home cages (4 h)
43	Flashing light (2 h)
44	Restraint (2 h)
45	Isolation
46	Isolation
47	Isolation
48	Damp bedding (2 h)
49	Inclination of home cages (6 h)
50	No stressor applied
51	Flashing light (2 h)
52	Water deprivation (24 h)
53	Restraint (3 h)
54	Damp bedding (3 h)
55	Inclination of home cages (4 h)
56	Cold restraint (2 h)

Table 2. Schedule of the different manipulation exerted on the animals subjected to the stress with or without curcumin or sertraline treatment

Manipulations	Day
Stress induction	0~56
Sucrose consumption test	34~40
Adaptation session of the radial maze test	41~42
Learning session of the radial maze test	43~56
Elevated plus maze test	57
No manipulation	58~67
Retention session of the radial maze test	68~69
Scarification	70

that would typically be attained with repeated training and would maintained from days to months [37, 38]. In the present study the Radial Arm Maze (RAM) has been designed to evaluate the learning and memory in rats. The apparatus consists of eight equidistantly spaced arms (42×12×12 cm^3). The arms were radiated from a central octagonal platform. The animals were assessed for learning and memory in a partially baited RAM. Prior to the training, the animals were kept on a restricted regime; so that their body weight would reach 85% of that prior to the training [37, 38].

Adaptation session

The animals were allowed to have two sessions of adaptation on two continuous days prior to the beginning of the learning period. During these adaptation sessions, the rats were allowed to explore the baited arms of the maze for 10 min.

Acquisition session

During the acquisition session (learning period), the animals were given two acquisition trials per day until they attained the learning criteria. The learning criteria were defined as follows. The trial was continued for 5 min and the training was continued until the rats reached the criteria of 80% correct choice; i.e., at least four correct entries out of five. This session lasted up to fifteen days. At the beginning of each trial, the maze was cleaned with ethanol (70%) and thereafter four of the arms (2, 3, 5, and 7) were baited with nourishment. The rat was placed on the central platform and was allowed to move freely. The arm choice was recorded when the rat ate bait or reached the end of an arm. Only the first entrance to the baited arm was recorded as a correct choice and the maze arms were not nourished again. Entrances into the unbaited arms and reentrances into the baited arms were recorded as Reference Memory Errors (RME) and Working Memory Errors (WME), respectively. Each rat was given two trials daily and the data obtained from the two trials were averaged and entered into the final data analysis. The rats' actions were scored by the percentage

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of the correct choices, RME, and WME [5, 37, 38].

Retention session

Ten days after acquisition, the rats were examined for retention of the task. The rats were given two trials, and the mean scores of the percentage of the correct choices, WME, and RME was used for analysis [5, 37, 38].

Assessment of behavior in the elevated plus maze

The elevated plus maze is a rodent model of anxiety. The test setting consists of a plus-shaped apparatus with two open and two enclosed arms, each with an open roof. The model is based on rodents' disgust of open spaces. Anxiety reduction in the plus-maze is defined by an increase in the time spent in the open arms and an increase in the entries into the open arms. Total number of arm entries and number of closed-arm entries are usually employed as measures of general activity [39]. In the present study for the elevated plus maze test, the rats were placed at the intersection of the four arms of the maze. The maze consisted of two open arms (50×10 cm^2) without walls and two opposite enclosed arms of the same size with 40 cm high walls. The maze was placed 50 cm above the floor in a quiet and dimly lit room. The rats got acclimatized to the testing room for at least 1 h before starting the test. The maze was cleaned after each testing. The animals were placed in the center of the maze facing an enclosed arm. Then, the number of entries into the enclosed or open arms and time spent in both open and enclosed arms were recorded for 5 minutes. The total number of entries into both enclosed and open arms was considered as the general motor activity [11, 39, 40].

Assessment of sucrose consumption

To evaluate anhedonia in the rats, during the sucrose consumption test, the rats were given. The rats were allowed to adapt to the two bottles of water for 7 days and further experimental manipulations were started after 7 days. The rats had a free choice between two bottles filled with tap water and 1%, 2%, 4%, 8%, 16%, 32%, and 64% sucrose in 7 consecutive days. The acceptable criterion for sucrose preference was consumption of 60% of total liquid intake. Non-preferring animals (10%) were excluded from the study. The consumption of water and sucrose solution was estimated simultaneously in the control and experimental groups by weighing the bottles. The sucrose intake was calculated as the amount of consumed sucrose in mg/gram body weight. In addition, the preference for sucrose was calculated as the percentage of consumed sucrose solution out of the total amount of the liquid which was drunk [41].

Statistical analysis

The data were analyzed using analysis of variance (ANOVA) followed by Tukey's test. All the values are expressed as mean±SD. Besides, $p \leq 0.05$ was considered as statistically significant.

RESULTS

Correct choices during the learning phase

On days 1~3, all the animals in each group showed similar learning performance in the radial maze (RAM), while they seemed to gradually improve their ability to learn the location of the baited arm during the learning phase from the 4th to the 8th day (Fig. 1).

A two-way repeated measures ANOVA was performed with training day as within-subjects factor and experimental group as between-subjects factor. A significant different was found for Day [($p<0.001$); $F(7, 483)=29.79$)], Group [($p<0.001$); $F(6, 63)=17.55$)], and the Day by Group interaction [($p<0.001$); $F(42, 483)=8.22$)].

This suggests that the performance of the animals changed during the acquisition and that this change in performance differed between the groups ($p<0.001$) (Fig. 1). Performance on 8th day was further analyzed to assess the group differences in learning

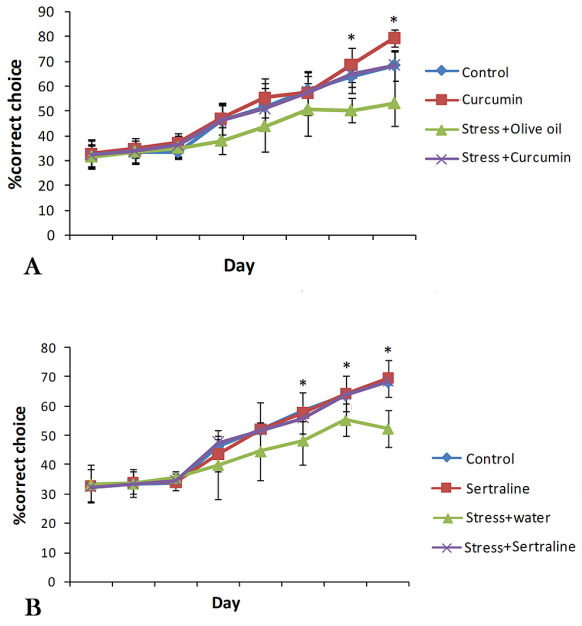

Fig. 1. The effects of sertraline and curcumin on the stress-induced learning and memory impairment in rats. Mean±SD of the percentage of the correct choices during the learning phase in the control, stressed, and non-stressed rats with or without curcumin (A) or sertraline (B) treatments.*$p<0.001$ (stress+curcumin *vs.* stress+olive oil), *$p<0.001$ (stress+sertraline *vs.* stress+water).

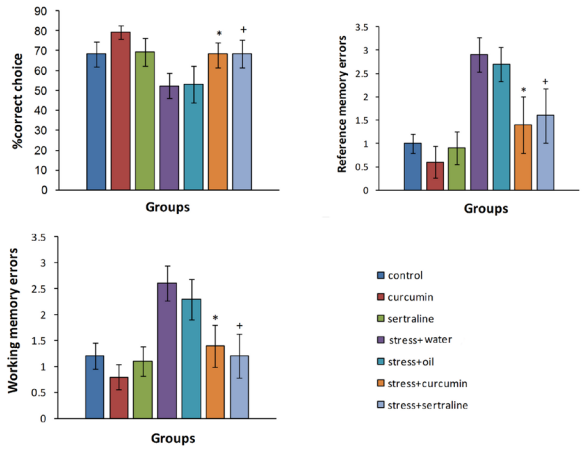

Fig. 2. The effects of sertraline and curcumin on the stress-induced learning and memory impairment in rats on day 8. Mean±SD of the percentage of the correct choices, reference and working memory errors during the learning phase in the control, stressed, and non-stressed rats with or without curcumin or sertraline treatments on day 8.*p<0.001 (stress+curcumin *vs.* stress+olive oil), +p<0.001 (stress+sertraline *vs.* stress+water).

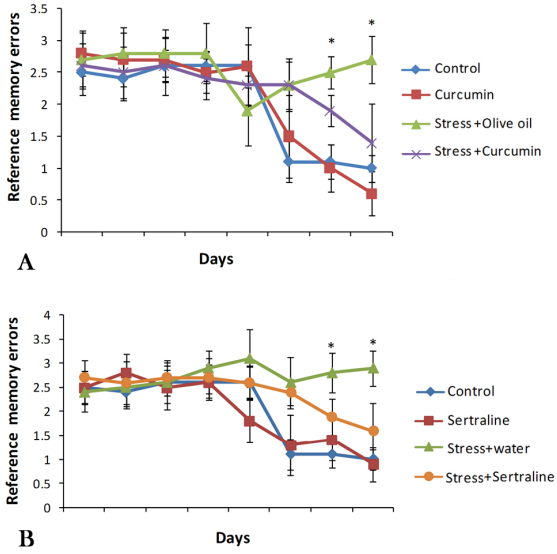

Fig. 3. The effects of sertraline and curcumin on the stress-induced learning and memory impairment in rats. Mean±SD of reference memory errors during the learning phase in the control, stressed, and non-stressed rats with or without curcumin (A) and sertraline (B) treatments. *p<0.001 (stress+curcumin *vs.* stress+olive oil), *p<0.001 (stress+sertraline *vs.* stress+water).

and a significant effect was found for groups at this time point [(p<0.001); F (6, 63)=7.66] (Fig. 2). The score of the correct choices were increased in the rats of the stress+curcumin, stress+sertraline groups in comparison to the stress+water and stress+olive oil groups (Fig. 1).

In comparison to the non-stressed rats, stress+water and stress +olive oil groups showed a significantly lower percent of correct choices from the 1st to 8th day (Fig. 1). However, no significant differences were found among the stress+curcumin, stress+sertraline and both compounds improved the rats' performance after stress (Fig. 1).

Reference memory errors during the learning phase

A significant effect was observed for Day [(p<0.001); F (7, 483)=8.02)], Group [(p<0.001); F (6, 63) =11.23)], and the Day by Group interaction [(p<0.001); F (42, 483)=5.67)].

This suggests that the RME during the acquisition phase changed with the days of training and these changes were different between the groups (Fig. 3).

Reference memory errors on 8th day were further analyzed to assess the group differences in learning and a significant effect was found for groups at this time point [(p<0.001); F (6, 63) =45.29] (Fig. 2). Moreover, stress+water and stress+olive oil groups revealed significantly more RME from the 1st to 8th day compared to non-stressed, stress+curcumin and stress+sertraline rats (p<0.001). Fewer errors were observed in evaluation of the reference memory in the rats of stress+curcumin and stress+sertraline groups in comparison to the stress+water and stress+olive oil groups (Fig. 3). Nevertheless, no significant differences were found among the stress+curcumin, stress+sertraline and both compounds improved the rats' performance after stress (Fig. 3).

Working memory errors during the learning phase

A two-way repeated measures ANOVA was performed with training day as within-subjects factor and experimental group as between-subjects factor. A significant effect was observed for Day [(p<0.001); F (7, 483)=7.86)], group [(p<0.001); F (6, 63) =13.53)] as well as the day by group interaction [(p<0.001); F (42, 483)=4.50)] (Fig. 4). Working memory errors on day 8 were further analyzed to assess the group differences in learning and a significant main effect was found for groups at this time point [(p<0.001); F (6, 63)=24.87)] (Fig. 2). Furthermore, stress+water and stress+olive oil groups showed a significantly more WME from the 1st to 8th day compared to non-stressed rats (p<0.001). Fewer errors were observed in evaluation of the working memory in the rats of stress+curcumin and stress+sertraline groups in comparison to the stress+water and stress+olive oil groups (Fig. 4). Nonetheless, no significant differences were found among the stress+curcumin, stress+sertraline and both compounds improved the rats' performance after stress (Fig. 4).

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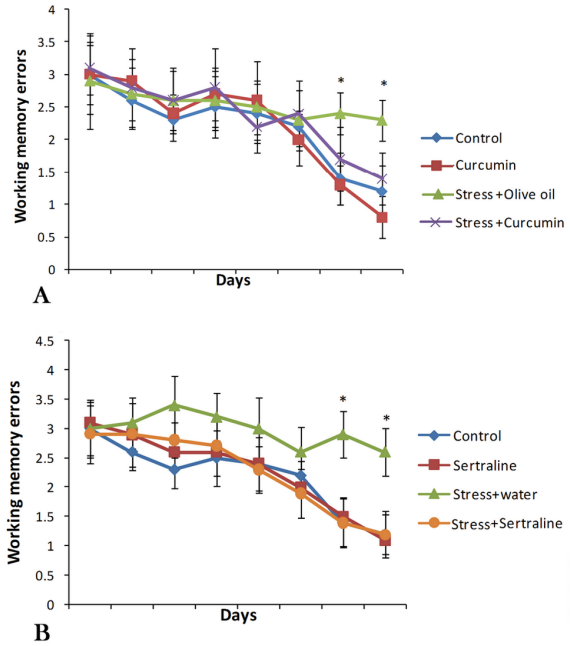

Fig. 4. The effects of sertraline and curcumin on the stress-induced learning and memory impairment in rats. Mean±SD of working memory errors during the learning phase in the control, stressed, and non-stressed rats with or without curcumin (A) and sertraline (B) treatments. *p<0.001 (stress+curcumin *vs.* stress+olive oil), *p<0.001 (stress+sertraline *vs.* stress+water).

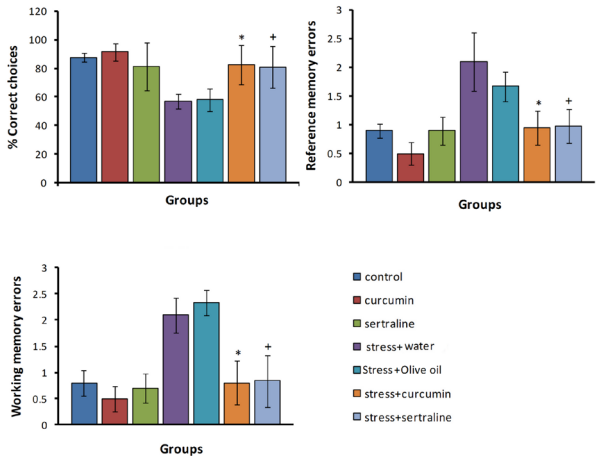

Fig. 5. The effects of sertraline and curcumin on the stress-induced learning and memory impairment in rats. Mean±SD of the percentage of the correct choices, reference and working memory errors during the retention phase in the control, stressed, and non-stressed rats with or without curcumin and sertraline treatments. *p<0.001 (stress+curcumin *vs.* stress+olive oil), *p<0.001 (stress+sertraline *vs.* stress+water).

Correct choices during retention testing

A one-way ANOVA was used to analyze the percentage of the correct choices during the retention session. A significant difference was found among the study groups regarding the percentage of correct choices [(p<0.001); F (6, 63)=16.17] (Fig. 5). Furthermore, the stress+water and stress+olive oil groups revealed a significant reduction in the percentage of the correct choices compared to the non-stressed rats (p<0.001). Nevertheless, no significant differences were found among the stress+curcumin, stress+sertraline and both compounds improved the rats' performance after stress (Fig. 5). This demonstrated that concomitant treatment of curcumin or sertraline during stress prevented the reduction of scores of the correct choices in the retention session.

Reference memory errors and working memory errors during retention testing

A significant difference was observed among the groups regarding the number of reference memory errors [(p<0.001); F (6, 63)=19.75], and the number of working memory errors (p<0.001). Besides, in comparison to the other groups, stress+water and stress+olive oil showed more RME and WME during the retention testing in comparison to the non-stressed rats (p<0.001) (Fig. 5). The concomitant treatment of curcumin or sertraline during stress causes fewer errors during evaluation of the reference and working memories in the retention session and they have similar effects (Fig. 5).

Performance in the elevated plus maze

ANOVA was performed on Open Arms Time (OAT) and Open Arms Entries (OAE), as measures of anxiety, and revealed a significantly lower percent of the OAT and OAE by the stress+water and stress+olive oil groups compared to the non-stressed rats [(p<0.001); F(6, 77)= 11.48]. Nevertheless, no significant differences were found among the stress+curcumin, stress+sertraline, and both compounds improved the rats' performance in OAT and OAE after stress (Fig. 6). ANOVA was also performed on closed arms entries and open arms entries, as a parameter reflecting the changes in the general motor activity, and showed no significant differences among the study groups (Fig. 6).

Sucrose consumption

The rats consumed almost less water in these tests and sucrose solution intake varied according to its concentration. Analysis of the data revealed that the rats drank more sucrose solution than water at the 4, 8, 16, 32, and 64% concentrations, while the difference was not significant at 1 and 2% concentrations. In contrast, the stress+water and stress+olive oil groups consumed more water than sucrose solution at 1~4% concentrations

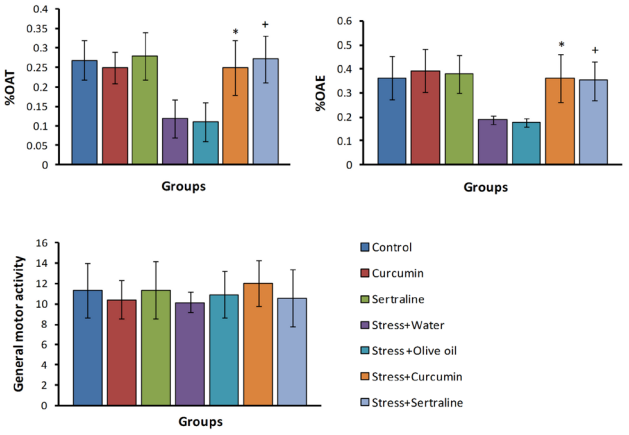

Fig. 6. The effects of sertraline and curcumin on the stress-induced anxiety in rats. Mean±SD of the percentage of time spent in the open arms (OAT), percentage of the number of open arm entrances (OAE), general motor activity measures in the elevated plus-maze test in the control, stressed, and non-stressed rats with or without curcumin or sertraline treatments. *p<0.001 (stress+curcumin *vs.* stress+olive oil), +p<0.001 (stress+sertraline *vs.* stress+water).

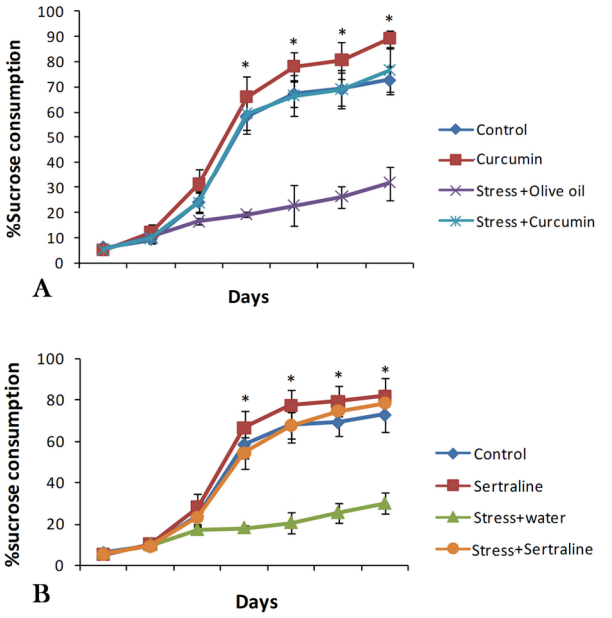

Fig. 7. The effects of sertraline and curcumin on the stress-induced anhedonia in rats. Mean±SD of the percentage of sucrose consumption out of total liquid consumption over the 7-day test period in the control, stressed, and non-stressed rats with or without curcumin (A) or sertraline (B) treatments. *p<0.001 (stress+curcumin *vs.* stress+olive oil), *p<0.001 (stress+sertraline *vs.* stress+water).

compared to 8, 16, 32, and 64% concentrations. Overall, as the concentration increased from 1% to 64%, the rats' total intake increased, as well. The results revealed no difference among stress+curcumin and stress+sertraline groups regarding sucrose preference. However, a significant decrease of sucrose preferences was observed in stress+water and stress+olive oil groups compared to the non-stressed groups (Fig. 7). Moreover, the results revealed a significant difference between stress+water and stress+olive oil groups compared to stress+curcumin and stress+sertraline groups; [(p<0.001) F(6, 77)=95.00].

DISCUSSION

The present study aimed to assess the effects of curcumin and sertraline treatment on the brain-dependent spatial learning and memory, anxiety, and anhedonia in the rats subjected to 56 days of chronic variable stress. The results of the present study supported the previous studies suggesting that chronic variable stress causes memory dysfunction, Anxiety and anhedonia in a rodent model [42-44].

Neurobiological and neurophysiologic evidences both in animal and in humans have displayed the role of monoaminergic system (catecholamine's and serotonin) in the pathophysiology of mental depression [45]. Previous studies also reported that antidepressants (imipramin, fluoxetine, desipramine, tranylcypromine, and curcumin) have a role in improving the memory and learning performance in animals as well as humans [16, 17, 25, 26]. The main finding of the present study was that curcumin and sertraline treatment improved the stress-induced cognitive impairment. The exact mechanism of the antidepressant and neuroregenerative ability of curcumin is not fully understood. However, it is hypothesized to act through inhibiting the monoamine oxidase enzyme and modulating the levels of serotonin and dopamine in the brain and prevent the stress-induced decrease in the serotonin level in the brain [16, 17, 23, 24]. There are some evidences which suggest that curcumin may work better than other antidepressants for some subtypes of depression because its side effects are much less pronounced [16, 17]. Wang et al. [46] have suggested the involvement of serotonin receptors in the antidepressant-like effect of curcumin.

The present work showed that the efficacy of curcumin in improvement of the behavioral changes in stressed rats was comparable to sertraline, a selective serotonin reuptake inhibitor antidepressant. Sertraline is used to treat major depression and many other neurodegenerative disorders [27-29]. The Previous studies also reported that SSRIs treatment significantly improved the performance of the rats in Morris water maze, sucrose consumption and elevated plus maze, suggesting its therapeutic potential in this disorder [18, 27, 28]. They also showed that

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sertraline treatment reduced acetylcholinestease enzyme levels in all regions of the brain, which is associated with improved memory performance in the animals [28, 29]. In addition, the results of the study by Inoue [47] showed that SSRIs inhibited the glutamatergic neurons of the brain through increased extracellular serotonin levels, which is in line with our study results.

Although benzodiazepines were the first-line drugs used to treat anxiety disorders, there are some limitations in their usage. They are not effective in some subtypes of anxiety disorders and exert side effects, such as dependency, somnolence, and memory disturbances [48]. However, selective serotonin reuptake inhibitors, which have less dependency, are effective for most subtypes of anxiety disorders and these compounds are now being used as anti-anxiety drugs as well as antidepressants [21].

Anhedonia was tested as the inability to experience pleasure from sucrose consumption. Previous studies also investigated the effect of fluoxetine, as an SSRI, on sucrose consumption in rats. According to the controversial results, fluxoetine treatment altered CNS 5-HT levels and, consequently reduction of the sucrose consumption in the animals can be seen [18]. In other study it has been shown that the sucrose solution intake was restored by treatment of antidepressant after chronic stress in rats [48]. Up to our knowledge, no research has been conducted on the effect of curcumin and sertraline on sucrose consumption up to now. Overall, the present study revealed the efficacy of curcumin and sertraline in improvement of sucrose consumption in a rodent model. However, the controversial conclusion might be due to different sucrose intake test, stress regimen and the strain of studied animals.

It has been reported that chronic stress causes impairment of memory tasks. Some brain areas including hippocampus, amigdala, medial prefrontal and entorhinal cortices are responsible for the related functions. The studies indicate that prolonged treatment by high glucocorticoid doses or stress induction is able to impair performance on more demanding tasks involving hippocampal function. Under these conditions there is no neuronal loss but there are reductions in volume of hippocampal neuropil that may be due to loss of glia cells or reduction of dendritic length and branching. It has been reported that stress can inhibit adult hippocampal neurogenesis [49], whereas antidepressant treatment has an opposite effect [50]. In addition, the patients with mood disorders often have smaller hippocampal volumes [51] rapidly led to the formulation of the "neurogenic hypothesis" of depression. Since then, this view has been refined. According to the current opinion, newborn hippocampal granule cells may not be critical contributors to the development of depression but nevertheless may be essential for certain behavioral antidepressant effects [50]. The demonstration that various antidepressant treatment strategies can stimulate neurogenesis in the adult dentate gyrus [29] has been followed by studies showing defeat [52]. It is, however, possible that the effect is not limited to the medial prefrontal cortex [53]. It has been shown a substantial decrease in cell proliferation in the primary motor cortex after 5weeks of social defeat stress, but the same paradigm had no effect on the survival rate of the newly generated cells in the same cortical area [54]. The generation of new neurons or glia is the end product of a series of steps consisting of proliferation, survival, migration, and differentiation and, with respect to neurons, the establishment of functional connections with other neurons.

CONCLUSION

In conclusion, the study findings showed that stressed animals that treated with curcumin and sertraline had better learning curves, more correct choices and fewer reference and working memory errors compared to the stressed rats without drugs treatments. Both curcumin and sertraline increased the percentage of open arms entries and time spent in the open arms of the stressed rats. In addition, both curcumin and sertraline improve the sucrose consumption in stressed rats and decrease anhedonia. It appears that curcumin and sertraline have the similar effectiveness on behavioral changes in chronic variable stress-induced rats.

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REFERENCES

1. de Kloet ER, Joëls M, Holsboer F (2005) Stress and the brain: from adaptation to disease. Nat Rev Neurosci 6:463-475.

2. Mizoguchi K, Yuzurihara M, Ishige A, Sasaki H, Chui DH, Tabira T (2000) Chronic stress induces impairment of spatial working memory because of prefrontal dopaminergic dysfunction. J Neurosci 20:1568-1574.
3. Kendler KS, Kessler RC, Walters EE, MacLean C, Neale MC, Heath AC, Eaves LJ (1995) Stressful life events, genetic liability, and onset of an episode of major depression in women. Am J Psychiatry 152:833-842.
4. Shelton CI (2004) Diagnosis and management of anxiety disorders. J Am Osteopath Assoc 104:S2-S5.
5. Karkada G, Shenoy KB, Halahalli H, Karanth KS (2012) Nardostachys jatamansi extract prevents chronic restraint stress-induced learning and memory deficits in a radial arm maze task. J Nat Sci Biol Med 3:125-132.
6. McEwen BS (2007) Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 87:873-904.
7. Aleisa AM, Alzoubi KH, Gerges NZ, Alkadhi KA (2006) Nicotine blocks stress-induced impairment of spatial memory and long-term potentiation of the hippocampal CA1 region. Int J Neuropsychopharmacol 9:417-426.
8. Gerges NZ, Alzoubi KH, Park CR, Diamond DM, Alkadhi KA (2004) Adverse effect of the combination of hypothyroidism and chronic psychosocial stress on hippocampus-dependent memory in rats. Behav Brain Res 155:77-84.
9. Lupien SJ, Gaudreau S, Tchiteya BM, Maheu F, Sharma S, Nair NP, Hauger RL, McEwen BS, Meaney MJ (1997) Stress-induced declarative memory impairment in healthy elderly subjects: relationship to cortisol reactivity. J Clin Endocrinol Metab 82:2070-2075.
10. Park CR, Campbell AM, Diamond DM (2001) Chronic psychosocial stress impairs learning and memory and increases sensitivity to yohimbine in adult rats. Biol Psychiatry 50:994-1004.
11. Sharma AC, Kulkarni SK (1992) Evaluation of learning and memory mechanisms employing elevated plus-maze in rats and mice. Prog Neuropsychopharmacol Biol Psychiatry 16:117-125.
12. Zhukov DA, Vinogradova KP (1994) Inescapable shock induces the opposite changes of the plus-maze test behavior in rats with divergent coping strategy. Physiol Behav 56:1075-1079.
13. Zurita A, Cuadra G, Molina VA (1999) The involvement of an opiate mechanism in the sensitized behavioral deficit induced by early chronic variable stress: influence of desipramine. Behav Brain Res 100:153-159.
14. Zurita A, Martijena I, Cuadra G, Brandão ML, Molina V (2000) Early exposure to chronic variable stress facilitates the occurrence of anhedonia and enhanced emotional reactions to novel stressors: reversal by naltrexone pretreatment. Behav Brain Res 117:163-171.
15. Alzoubi KH, Abdul-Razzak KK, Khabour OF, Al-Tuweiq GM, Alzubi MA, Alkadhi KA (2013) Caffeine prevents cognitive impairment induced by chronic psychosocial stress and/or high fat-high carbohydrate diet. Behav Brain Res 237:7-14.
16. Kulkarni S, Dhir A, Akula KK (2009) Potentials of curcumin as an antidepressant. ScientificWorldJournal 9:1233-1241.
17. Kulkarni SK, Bhutani MK, Bishnoi M (2008) Antidepressant activity of curcumin: involvement of serotonin and dopamine system. Psychopharmacology (Berl) 201:435-442.
18. Prendergast MA, Yells DP, Balogh SE, Paige SR, Hendricks SE (2002) Fluoxetine differentially suppresses sucrose solution consumption in free-fed and food-deprived rats--reversal by amantadine. Med Sci Monit 8:BR385-BR390.
19. Brouet I, Ohshima H (1995) Curcumin, an anti-tumour promoter and anti-inflammatory agent, inhibits induction of nitric oxide synthase in activated macrophages. Biochem Biophys Res Commun 206:533-540.
20. Jyoti A, Sethi P, Sharma D (2009) Curcumin protects against electrobehavioral progression of seizures in the iron-induced experimental model of epileptogenesis. Epilepsy Behav 14:300-308.
21. Tajima O (2004) Recent trends in pharmacotherapy for anxiety disorders. Nihon Shinkei Seishin Yakurigaku Zasshi 24:133-136.
22. Noorafshan A, Ashkani-Esfahani S (2013) A review of therapeutic effects of curcumin. Curr Pharm Des 19:2032-2046.
23. Xu Y, Ku BS, Yao HY, Lin YH, Ma X, Zhang YH, Li XJ (2005) The effects of curcumin on depressive-like behaviors in mice. Eur J Pharmacol 518:40-46.
24. Xu Y, Ku B, Cui L, Li X, Barish PA, Foster TC, Ogle WO (2007) Curcumin reverses impaired hippocampal neurogenesis and increases serotonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats. Brain Res 1162:9-18.
25. Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, Ritz L, Biggs MM, Warden D, Luther JF, Shores-Wilson K, Niederehe G, Fava M; STAR*D Study Team (2006) Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 354:1231-1242.
26. Barros DM, Izquierdo LA, Medina JH, Izquierdo I (2002) Bupropion and sertraline enhance retrieval of recent and remote long-term memory in rats. Behav Pharmacol 13:215-

 http://dx.doi.org/10.5607/en.2013.22.2.96

220.
27. Matar MA, Cohen H, Kaplan Z, Zohar J (2006) The effect of early poststressor intervention with sertraline on behavioral responses in an animal model of post-traumatic stress disorder. Neuropsychopharmacology 31:2610-2618.
28. Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301:805-809.
29. Malberg JE, Eisch AJ, Nestler EJ, Duman RS (2000) Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 20:9104-9110.
30. Lalonde R, Strazielle C (2010) Relations between open-field, elevated plus-maze, and emergence tests in C57BL/6J and BALB/c mice injected with GABA- and 5HT-anxiolytic agents. Fundam Clin Pharmacol 24:365-376.
31. Green AD, Barr AM, Galea LA (2009) Role of estradiol withdrawal in 'anhedonic' sucrose consumption: a model of postpartum depression. Physiol Behav 97:259-265.
32. Jain SK, Rains J, Croad J, Larson B, Jones K (2009) Curcumin supplementation lowers TNF-alpha, IL-6, IL-8, and MCP-1 secretion in high glucose-treated cultured monocytes and blood levels of TNF-alpha, IL-6, MCP-1, glucose, and glycosylated hemoglobin in diabetic rats. Antioxid Redox Signal 11:241-249.
33. Gupta YK, Briyal S, Sharma M (2009) Protective effect of curcumin against kainic acid induced seizures and oxidative stress in rats. Indian J Physiol Pharmacol 53:39-46.
34. Kheradpezhouh E, Panjehshahin MR, Miri R, Javidnia K, Noorafshan A, Monabati A, Dehpour AR (2010) Curcumin protects rats against acetaminophen-induced hepatorenal damages and shows synergistic activity with N-acetyl cysteine. Eur J Pharmacol 628:274-281.
35. Yildirim E, Erol K, Ulupinar E (2012) Effects of sertraline on behavioral alterations caused by environmental enrichment and social isolation. Pharmacol Biochem Behav 101:278-287.
36. Tagliari B, Noschang CG, Ferreira AG, Ferrari OA, Feksa LR, Wannmacher CM, Dalmaz C, Wyse AT (2010) Chronic variable stress impairs energy metabolism in prefrontal cortex and hippocampus of rats: prevention by chronic antioxidant treatment. Metab Brain Dis 25:169-176.
37. Dudchenko PA (2004) An overview of the tasks used to test working memory in rodents. Neurosci Biobehav Rev 28:699-709.
38. Srikumar BN, Raju TR, Shankaranarayana Rao BS (2006) The involvement of cholinergic and noradrenergic systems in behavioral recovery following oxotremorine treatment to chronically stressed rats. Neuroscience 143:679-688.
39. Hogg S (1996) A review of the validity and variability of the elevated plus-maze as an animal model of anxiety. Pharmacol Biochem Behav 54:21-30.
40. Costa R, Tamascia ML, Nogueira MD, Casarini DE, Marcondes FK (2012) Handling of adolescent rats improves learning and memory and decreases anxiety. J Am Assoc Lab Anim Sci 51:548-553.
41. Sclafani A, Ackroff K (2003) Reinforcement value of sucrose measured by progressive ratio operant licking in the rat. Physiol Behav 79:663-670.
42. Ivy AS, Rex CS, Chen Y, Dubé C, Maras PM, Grigoriadis DE, Gall CM, Lynch G, Baram TZ (2010) Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. J Neurosci 30:13005-13015.
43. Gouirand AM, Matuszewich L (2005) The effects of chronic unpredictable stress on male rats in the water maze. Physiol Behav 86:21-31.
44. Pellow S, Chopin P, File SE, Briley M (1985) Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci Methods 14:149-167.
45. Elhwuegi AS (2004) Central monoamines and their role in major depression. Prog Neuropsychopharmacol Biol Psychiatry 28:435-451.
46. Wang R, Xu Y, Wu HL, Li YB, Li YH, Guo JB, Li XJ (2008) The antidepressant effects of curcumin in the forced swimming test involve 5-HT1 and 5-HT2 receptors. Eur J Pharmacol 578:43-50.
47. Inoue T (2012) Pharmacotherapy of anxiety disorders. Seishin Shinkeigaku Zasshi 114:1085-1092.
48. Pothion S, Bizot JC, Trovero F, Belzung C (2004) Strain differences in sucrose preference and in the consequences of unpredictable chronic mild stress. Behav Brain Res 155:135-146.
49. Gould E, Tanapat P, McEwen BS, Flügge G, Fuchs E (1998) Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc Natl Acad Sci U S A 95:3168-3171.
50. Sahay A, Hen R (2007) Adult hippocampal neurogenesis in depression. Nat Neurosci 10:1110-1115.
51. Campbell S, Marriott M, Nahmias C, MacQueen GM (2004) Lower hippocampal volume in patients suffering from depression: a meta-analysis. Am J Psychiatry 161:598-607.
52. Thomas RM, Hotsenpiller G, Peterson DA (2007) Acute psychosocial stress reduces cell survival in adult hippocampal

neurogenesis without altering proliferation. J Neurosci 27:2734-2743.

53. Banasr M, Valentine GW, Li XY, Gourley SL, Taylor JR, Duman RS (2007) Chronic unpredictable stress decreases cell proliferation in the cerebral cortex of the adult rat. Biol Psychiatry 62:496-504.

54. Czéh B, Müller-Keuker JI, Rygula R, Abumaria N, Hiemke C, Domenici E, Fuchs E (2007) Chronic social stress inhibits cell proliferation in the adult medial prefrontal cortex: hemispheric asymmetry and reversal by fluoxetine treatment. Neuropsychopharmacology 32:1490-1503.

http://dx.doi.org/10.5607/en.2013.22.2.96