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Taurine Ameliorates Dementia Induced By Scopolamine In Male Wistar Rats

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Abstract

The current study investigates the anti-amnesic effect of taurine using scopolamine induced dementia rat model. Rats were divided into control, dementia rat model induced by daily treatment with scopolamine for 14 days and rats co-treated daily with taurine and scopolamine for 14 days. At the end of the experiment, dementia was evaluated behaviorally by novel object recognition test (NORT). The neurochemical changes induced in the cortex and hippocampus were assessed by measuring norepinephrine (NE), dopamine (DA), serotonin (5-HT), monoamine oxidase (MAO), acetylcholinesterase (AChE), Na+,K+,ATPase, oxidative stress parameters including malondialdehyde (MDA), nitric oxide (NO), and reduced glutathione (GSH), interleukin-1α (IL-1α), and interleukin-6 (IL-6).

In NORT data showed impaired memory in rats treated with scopolamine as indicated by the significantly decreased recognition index (RI) and the negative value of the discrimination ratio (DR). A significant increase in DA, MDA, NO, AChE, MAO, IL-1α, and IL-6 and a significant decrease in NE, GSH, and Na+,K+,ATPase were recorded in the cortex and hippocampus of rat model of dementia. Protection with taurine prevented the dementia as indicated by the control-like value of RI and the positive value of DR. This was mediated by the protective effect of taurine against the changes in DA, NE, MAO, AChE and Na+,K+,ATPase induced by scopolamine in the selected brain regions. In addition, taurine showed ameliorative effect against the oxidative stress and the neuroinflammation induced in the cortex and hippocampus by scopolamine. It is clear from the present behavioral and neurochemical findings that taurine has anti-amnesic effect against scopolamine induced dementia in rats. This effect could be attributed to the antioxidant and anti-inflammatory effects of taurine. In addition, the ability of taurine to prevent the cortical and hippocampal changes in NE and DA induced by scopolamine has a substantial role in its anti-amnesic effect.

Keywords: Dementia, Taurine; Oxidative stress; Neuroinflammation; Monoamines, Rats

1. Introduction

Dementia is used to indicate a reduction in the mental capacity related to memory, cognition, or other thinking abilities [1]. Dementia, affecting over 55 million individuals globally, is the seventh leading cause of mortality and a major cause of disability and dependency among older people (WHO 2021). Alzheimer's disease (AD) is a common kind of dementia and a progressive neurodegenerative disorder. Globally, it represents approximately 70% of all cases of dementia [2]. Cognitive dysfunction may arise congenitally or as a result of environmental factors such as toxicity, mental illness, and brain injuries [3]. It may also be caused by physiological factors such as inflammation, stress, and neurological disorders. Recently, other factors have been reported to impair memory, such as the massive use of cellular phones [4,5], and bad habits such as sleep deprivation (staying up) [6]. It has also been demonstrated that noise, a stressful environmental stimulus, causes cognitive deficits in memory formation, consolidation, and recall [7,8]. Multiple neuronal pathways and neurotransmitter systems are implicated in the process of learning and memory. According to experimental and clinical evidence, the central cholinergic system has a crucial role in the regulation of cognitive functions [9,10]. It has been reported that low acetylcholine (ACh) levels cause memory loss [11]. Choline uptake and ACh synthesis are reduced in the cerebral cortex and hippocampus. On the other hand, enhanced expression of acetylcholinesterase (AChE), an enzyme that metabolizes ACh, has been recorded in patients suffering from dementia [12]. In addition, the monoamine neurotransmitter system can also modulate memory and cognition. These neurotransmitters include serotonin, norepinephrine, and dopamine [13,14]. Oxidative stress and neuronal loss, especially in the hippocampus, are implicated in the impairment of memory and cognitive processes [15]. Moreover, neuroinflammatory processes have been implicated in the pathogenesis of dementia [16]. IL-6 has been observed to negatively

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affect memory formation [17]. Recently, it has been suggested that blocking the pro-inflammatory IL-6 signaling ameliorates impaired memory and metabolic alterations in dementia [18]. Additionally, it has been observed that IL-1 has a role in age-related memory impairments [19]. Reducing IL-1α release may provide new therapeutic targets for the treatment of life-threatening acute brain injuries [20].

Dementia represents the highest economic cost of adult neurological diseases. It is estimated that the costs of the management and treatment of dementia range from USD 600 billion to one trillion USD. Therefore, it is crucial to find the proper measures to avoid the expansion of the disease [21]. Up till now, cholinesterase inhibitors have been the main therapeutic strategy for symptomatic treatment [22]. They act by enhancing cholinergic neurotransmission through reducing excessive hydrolysis of ACh by AChE. However, these drugs have a modest therapeutic effect, and the persistence of their effects and long-term safety are unknown. N-methyl-D-aspartate (NMDA) receptor antagonists are also used as therapeutic agents against memory and cognitive impairment. Unfortunately, these agents have several side effects, including sleep disorders and nausea, as well as their short half-lives [23], which may be induced as a result of their non-selective action on different tissues both centrally and peripherally [24]. Thus, it is substantial to search for a long-lasting, efficient substitute method to treat or prevent dementia. Taurine is a sulfur-containing β-amino acid involved in a variety of biological functions, including retinal and CNS development, neuromodulation, membrane stabilization, osmoregulation, calcium homeostasis, antioxidant functions, and neuroprotection [25-28]. Taurine depletion has been found to raise the risk of various diseases such as AD, Parkinson's disease, cardiovascular disorders, diabetes, and retinal neuronal deteriorations [29]. It has been found that taurine ameliorates Aβ1-42-induced cognitive impairments, as well as neuronal damage in AD transgenic mice model. These actions were attributed to its neuroprotective and antioxidant effects [30]. However, more research is needed to fully understand taurine's possible therapeutic and preventive properties against scopolamine-induced Aβ accumulation.

Scopolamine can produce impaired memory and cognitive functions similar to those observed in the elderly. Scopolamine, a nonselective, and competitive inhibitor of the muscarinic acetylcholine receptor is involved in working memory. It blocks muscarinic acetylcholine receptors, and causes temporary blockage in neuronal signal transmission, and subsequently resulting in learning and memory disturbance [31]. As a result, scopolamine can produce both peripheral antimuscarinic properties and central sedative, antiemetic, and amnestic effects [32]. Scopolamine exerts its antiemetic effect by blocking the muscarinic receptors in the medulla oblongata. These alterations are caused by increasing the activity of AChE and decreasing choline acetyltransferase activity, ACh level and the antioxidant mechanisms in the brain of mouse model of dementia induced by scopolamine [33,34]. The oxidative stress induced in the brain by scopolamine has been observed by several studies [35,36]. Thus, scopolamine is usually used to induce cognitive deficits in healthy animals and produce an animal model of AD and also to evaluate the cognition-enhancing properties of new drugs [37].

The current study was designed to evaluate the neuroprotective effects of taurine versus the behavioral as well as the cortical and hippocampal neurochemical alterations induced by scopolamine in a rat model of dementia.

2. Materials and Methods

Animals

Twenty-four Wistar adult male albino rats (180 – 200 g) were used in the present research. They were purchased from the animal house of the National Research Centre, Egypt. Rats were placed in plastic cages in a chemical-free environment that was artificially lit (12 hours of light and dark cycles) and temperature-controlled (20–25 °C). They were also given free access to tap water and standard laboratory food. Animal procedures were carried out in compliance with the instructions of the National Institute of Health Guide for Care and Use of Laboratory Animals (publication no. 85-23, revised 1985).

Chemicals and drugs

Taurine and scopolamine hydrobromide were purchased from Sigma-Aldrich (St. Louis, MO, USA). Scopolamine and taurine were dissolved in saline solution (0.9%). The other chemicals used in the current study were of the highest analytical grade.

2.1. Experimental Design

After an acclimatization period of one week, twenty-four rats were divided into three groups. Control rats (n=8) received daily intraperitoneal (i.p) injection of physiological saline solution (0.9%) till the end of the experiment. The second group (n=8) was the rat model of dementia that induced by daily i.p injection of scopolamine (3 mg/kg) for 14 days Liao et al. [38]. The third group (n=8) received a daily i.p. injection of taurine (100 mg/kg) [28] prior to scopolamine injection (the time interval between the two treatments was one hour) for 14 days.

2.2. Behavioural analysis

2.2.1. Novel object recognition test

NORT depends on the innate predisposition of rats to explore a novel object more than an older object [39]. This test is performed over three successive days in three phases using a wooden box (30 × 30 × 30). The habituation phase is the first phase during which each rat was allowed to adapt with the surrounding box for ten minutes. The training phase was carried out in the second day during which rats were allowed to familiarize with two wooden objects made from non-toxic materials and having the same size, shape and color. These objects were positioned inside the box in opposite corners 2 cm away from the walls. Each rat was allowed to stay 10 minutes in the box to identify and recognize the two identical objects. In the third day, which is the test phase, a novel object having a different size, shape and color was used to replace one of the two identical objects. Then, each rat was allowed to explore the novel and old objects for 5 minutes. After each rat, the wooden box and objects were cleaned thoroughly with 70% ethanol to remove the effect of odor cues. The recognition index (RI) represented the time spent by the rats to explore the novel object (N) as a percentage of the total exploration time spent by the rats to explore both the novel and familiar (N+F) objects.

$$\text{RI} = \frac{\text{Novel object exploration time (N)}}{\text{Total time of exploration (N+F)}} \times 100$$

The discrimination ratio (DR) is considered the difference between the time spent exploring the novel (N) and familiar (F) objects divided by the total time spent exploring both objects. The value can fall between +1 and −1 where the positive value means more time spent with the novel object, while the negative value indicates more time spent with the familiar object, and the zero score is a null preference.

$$\text{DR}=\frac{\text{Difference between exploration time of novel and familiar objects (N−F)}}{\text{Total time of exploration (N+F)}}$$

The novel object recognition test was performed on the last three successive days of the experimental period.

2.3. Preparation of samples

After carrying out NORT, rats were sacrificed. Then the brain of each rat was excised out and divided into two longitudinal halves; right and left. The cortex and hippocampus were dissected from each half. Each brain region was weighed and kept frozen at –80 °C until analysis. Each of the right cortex and hippocampus was homogenized using a sonicator in Tris–HCl buffer (pH 7.4). The homogenate was centrifuged and the supernatant of each sample was used to measure the enzyme activities, oxidative stress parameters, and interleukins (IL-1α and IL-6). Each of the cortex and hippocampus of the left halves was homogenized by a sonicator in an acidified *n*-butanol to determine monoamines.

2.3.1. Lipid Peroxidation assaying

Malondialdehyde (MDA) is a lipid peroxidation marker. It was determined in each brain region according to Ruiz-Larrea et al. [40]. In this method, thiobarbituric acid reacts with MDA in an acidic medium in boiling water bath for 20 min producing thiobarbituric acid reactive species, a pink colored complex, whose absorbance was read at 532 nm.

2.3.2. Nitric Oxide measurement (NO)

In the cortex and hippocamps, the level of NO was measured depending on the method of Montgomery and Dymock [41]. The level of endogenous nitrite was measured as a marker of NO production. The addition of Griess reagent converts nitrite into a deep purple-colored azo compound. The absorbance of the resultant dye was measured at 540 nm.

Determination of Reduced Glutathione

The estimation of reduced glutathione (GSH) was based on the spectrophotometric method described by Beutler et al. [42]. In this method, GSH was used to reduce 5, 5′ dithiobis-(2-nitrobenzoic acid) or DTNB “Ellman’s reagent” yielding the yellow chromogen 5'-thio-2-nitrobenzoic acid (TNB) whose absorbance was read at 412 nm.

2.3.3. Determination of Na,K,ATPase Activity

Na,K,ATPase activity in the selected brain areas was determined according to the method described by Tsakiris et al. [43]. The difference between total ATPase activity (Na,K,ATPase and Mg,ATPase activities) and Mg,ATPase activity represented Na,K,ATPase activity.

2.3.4. Determination of Acetylcholinesterase Activity

The measurement of acetylcholinesterase (AChE) activity in the selected brain areas was performed according to the modification of Ellman's method [44] by Gorun et al. [45]. AChE hydrolyzes acetylthiocholine iodide forming thiocholine which reacted with 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB). The absorbance of the produced yellow colored compound 5-mercapto-2-nitrobenzoic acid was measured at 412 nm.

2.3.5. Determination of Monoamine Oxidase Activity

Monoamine oxidase (MAO) activity was determined in the cortex and hippocampus according to the method of Holt et al. [46]. In this method, benzylamine is converted to benzaldehyde whose absorbance was read at 250 nm.

2.3.6. Determination of Interleukin-1α (IL-1α)

The measurement of interleukin-1α (IL-1α) levels in the cortex and hippocampus was carried out using rat ELISA kit supplied by Bioneovan Co., Ltd. (China). The absorbance of the developed color was read using a microtiter plate reader set at 450 nm. The concentration was then calculated from a standard curve. The concentration of IL-1α was expressed in pg/g brain tissue.

2.3.7. Determination of Interleukin-6 (IL-6)

Interleukin-6 (IL-6) was estimated in selected brain regions using rat ELISA Kit purchased from Bioneovan Co., Ltd. (China). The absorbance of the developed color was read at 450 nm using a microtiter plate. The concentration of IL-6 was expressed in pg/g brain tissue.

2.3.8. Determination of Monoamines

The levels of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) were measured in the cortex and hippocampus using the fluorometric method described by Ciarlone [47]. In this method, monoamines were extracted in butanol, then returned to an aqueous phase. They were then oxidized to a fluorescent derivative, the fluorescence of which was read using a spectrofluorometer (Jasco FP-6500, JASCO Ltd., Tokyo, Japan) supplied with a source of xenon arc lamp 150 W (excitation

monochromator had an excitation slit band width of 5 nm, and emission monochromator had an emission slit band width of 5 nm).

2.4. Statistical Analysis

The present data were expressed as means ± S.E.M. The statistical difference between the groups under investigation was carried out using one-way analysis of variance (ANOVA) followed by Duncan as post hoc test. The difference was considered significant at p-value < 0.05. Statistical Package for Social Sciences (SPSS) software was used for all statistical calculations.

3. Results

3.1. Novel object recognition test

The rat model of dementia showed a significant decrease in the recognition index (RI) recording -62.911% less than the control value. However, treatment with taurine ameliorated the decline in RI induced by scopolamine (Fig. 1). The discrimination ratio (DR) recorded -0.442 in the rat model of dementia. However, in control and taurine-treated rats, the DR recorded +0.502 and +0.406, respectively (fig. 1).

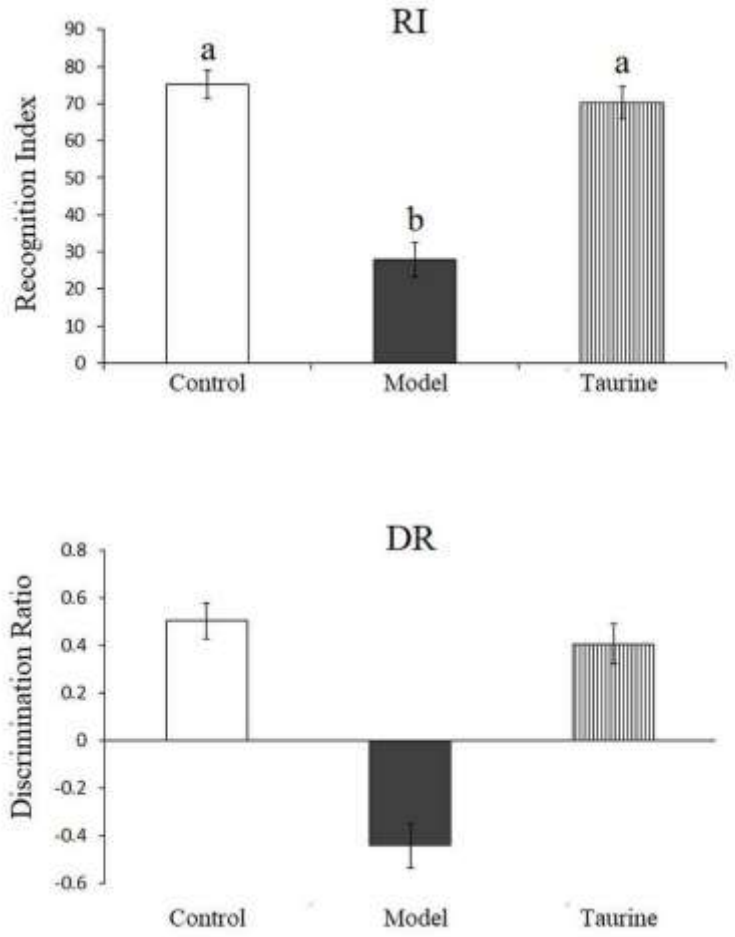

Fig.1: Effect of taurine (100 mg/kg) on the novel object recognition test parameters of rat model of dementia induced by scopolamine. Different letters indicate a significant change at P-value < 0.05 and similar letters mean nonsignificant changes between groups.

3.2. Oxidative stress parameters

In the rat model of dementia induced by scopolamine, a significant increase in cortical MDA (+42.86%) and NO (+54.55%) levels was recorded with respect to control levels. This was accompanied by a significant decrease in GSH level by 27.96%. Protection with taurine attenuated the significant increase induced by scopolamine in cortical MDA level and ameliorated the increase in NO levels. Although the cortical GSH level was improved by taurine from −27.96% to −12.90%, it still showed a significant decrease as compared to control (Fig. 2).

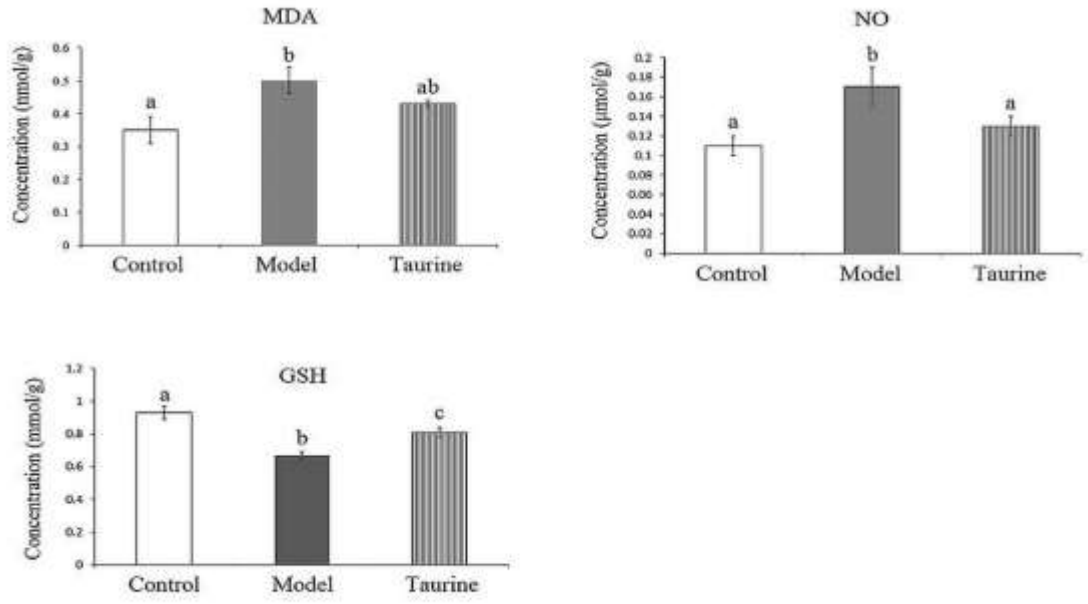

Fig.2: Effect of taurine (100 mg/kg) on the level of malondialdehyde (MDA), nitric oxide (NO) and reduced glutathione (GSH) in the cortex of rat model of dementia induced by scopolamine
Different letters indicate a significant change at P-value < 0.05 and similar letters mean nonsignificant changes between groups.

In the hippocampus of rat model of dementia, MDA and NO increased significantly recording +84.07% and +47.06%, respectively, as compared to control rats. However, GSH decreased significantly by 17.50%. Taurine pretreatment prevented the changes induced by scopolamine in hippocampal MDA, NO and GSH levels that showed control-like values (Fig. 3).

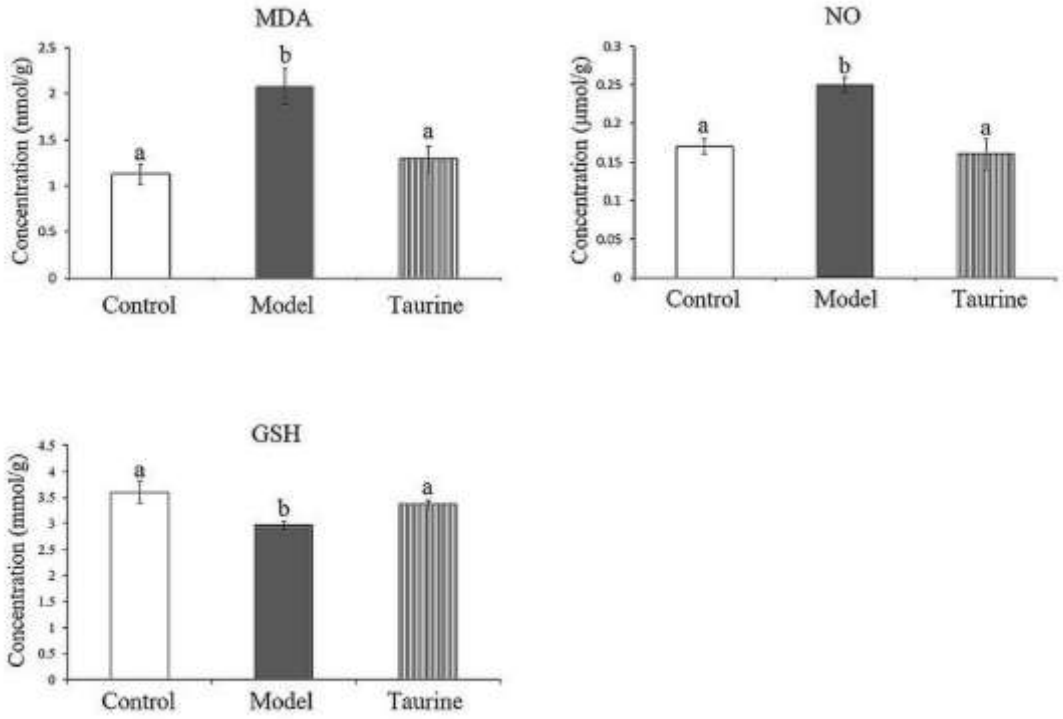

Fig.3: Effect of taurine (100 mg/kg) on the levels of malondialdehyde (MDA), nitric oxide (NO) and reduced glutathione (GSH) in the hippocampus of rat model of dementia induced by scopolamine
Different letters indicate a significant change at P-value < 0.05 and similar letters mean nonsignificant changes between groups.

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3.3. Enzymes activities

Data illustrated in Fig. (4) revealed that in the cortex of rat model of dementia induced by scopolamine, Na,K,ATPase activity decreased significantly by 27.27% and AChE and MAO activities increased significantly by 29.76% and 34.61, respectively, as compared to control values. Taurine pretreatment prevented the cortical changes in these enzyme activities (Figure 4).

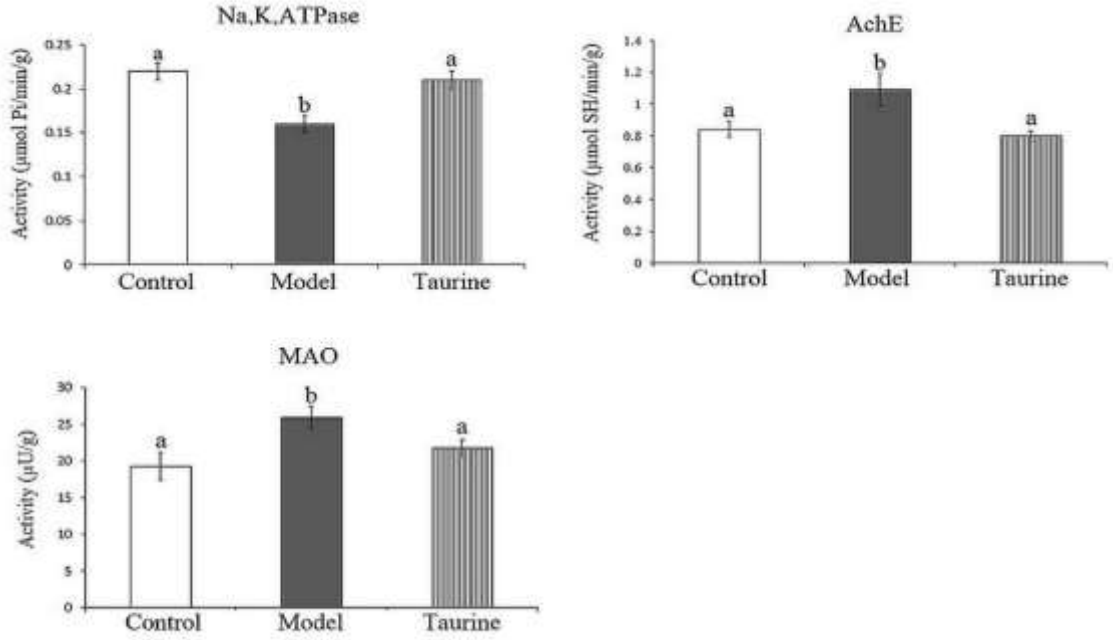

Fig.4: Effect of taurine (100 mg/kg) on the activities of Na,K,ATPase, acetylcholinesterase (AChE) and monoamine oxidase (MAO) in the cortex of rat model of dementia induced by scopolamine
Different letters indicate a significant change at P-value < 0.05 and similar letters mean nonsignificant changes between groups.

Similarly, in the hippocampus of dementia rat model, the activity of Na,K,ATPase decreased significantly by 26.32% and the activities of AChE and MAO increased significantly by 37.14% and 37.28%, respectively, as compared to control values. Protection with taurine succeeded in ameliorating scopolamine-induced variations in the hippocampal Na,K,ATPase, AChE and MAO activities (Fig. 5).

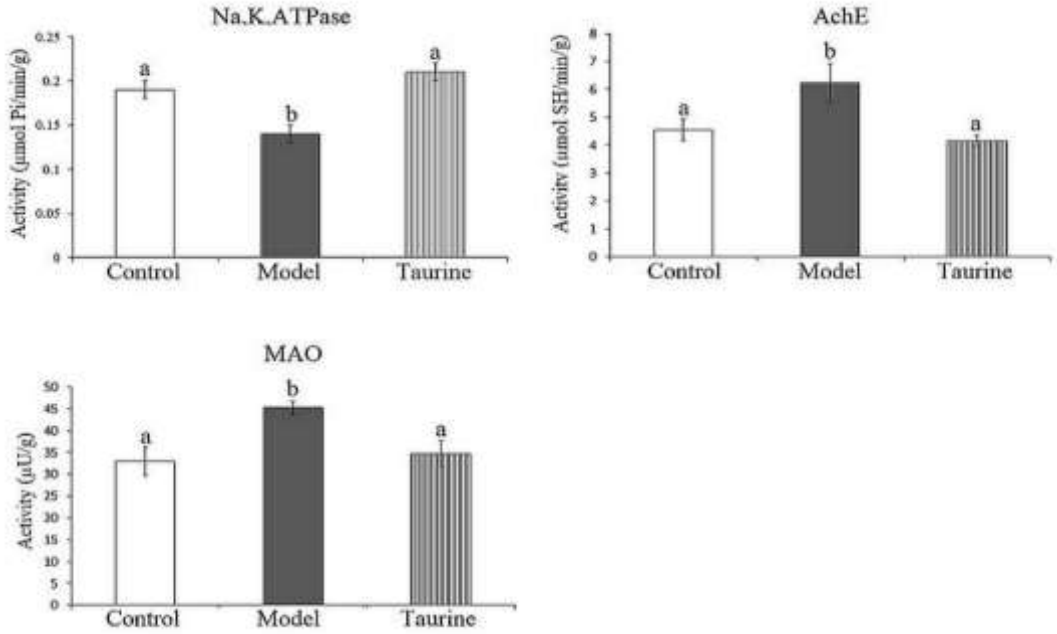

Fig.5: Effect of taurine (100 mg/kg) on the activities of Na,K,ATPase, acetylcholinesterase (AChE) and monoamine oxidase (MAO) in the hippocampus of rat model of dementia induced by scopolamine
Different letters indicate a significant change at P-value < 0.05 and similar letters mean nonsignificant changes between groups.

3.4. Interleukin-1α (IL-1α) and Interleukin-6 (IL-6)

In the rat model of dementia, the cortical IL-1α showed no significant change as compared to control. However, the daily i.p. injection of scopolamine significantly increased cortical IL-6 level by +106.24% as compared to the control value. The daily pretreatment of rat with taurine prevented the recorded increase in cortical IL-6 induced by scopolamine (Fig. 6).

The present results revealed a significant increase in IL-1α (+18.20%) and IL-6 (+54.25%) levels in the hippocampus of rat model of dementia as compared to control rats. Taurine protection prevented the significant increased level of IL-6 and failed to prevent the significant increase in IL-1α level in the hippocampus (Fig. 6).

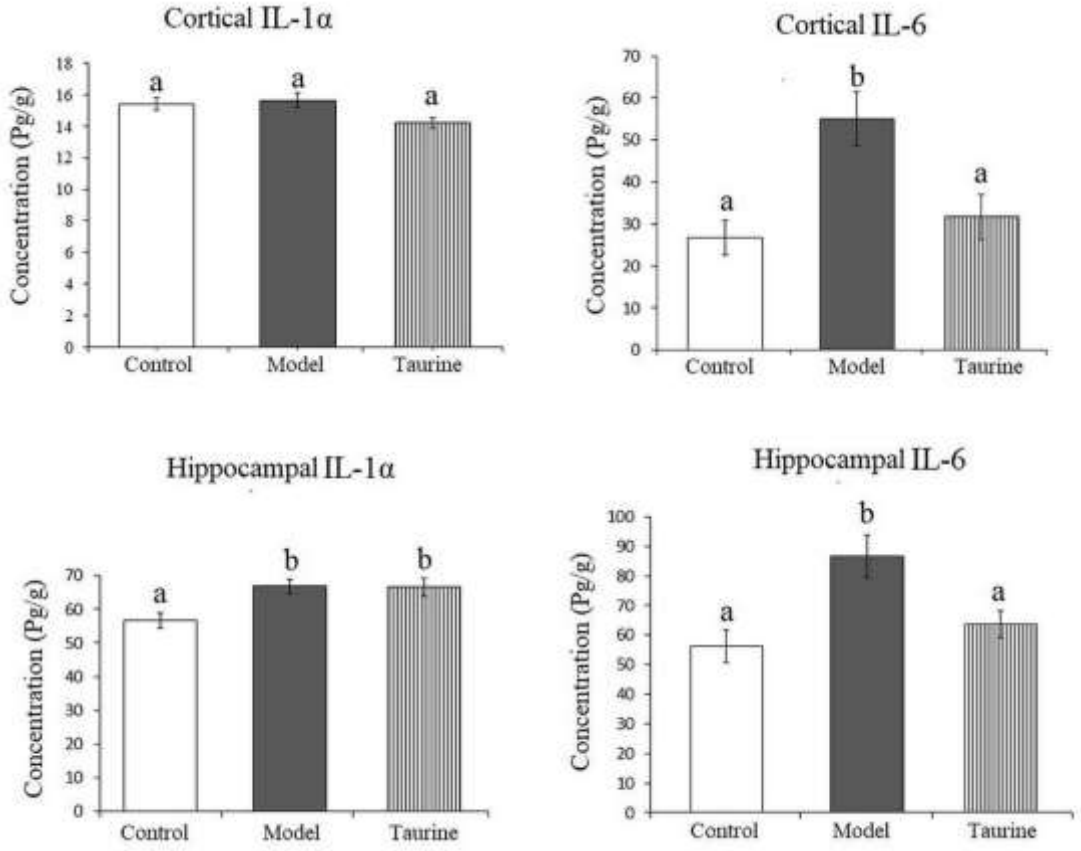

Fig.6: Effect of taurine (100 mg/kg) on the levels of interleukin-1α (IL-1α) and interleukin-6 (IL-6) in the cortex and hippocampus of rat model of dementia induced by scopolamine

Different letters indicate a significant change at P-value < 0.05 and similar letters mean nonsignificant changes between groups.

3.5. Monoamine neurotransmitters

As illustrated in Fig. (7), the present results revealed non-significant changes in 5-HT levels in the cortex of rat model of dementia. The daily i.p injection of scopolamine for 14 days decreased significantly the cortical level of NE by 25.89% and increased significantly DA level by 39.83% as compared to the cortical control levels. Taurine pretreatment prevented scopolamine-induced cortical changes in NE and DA.

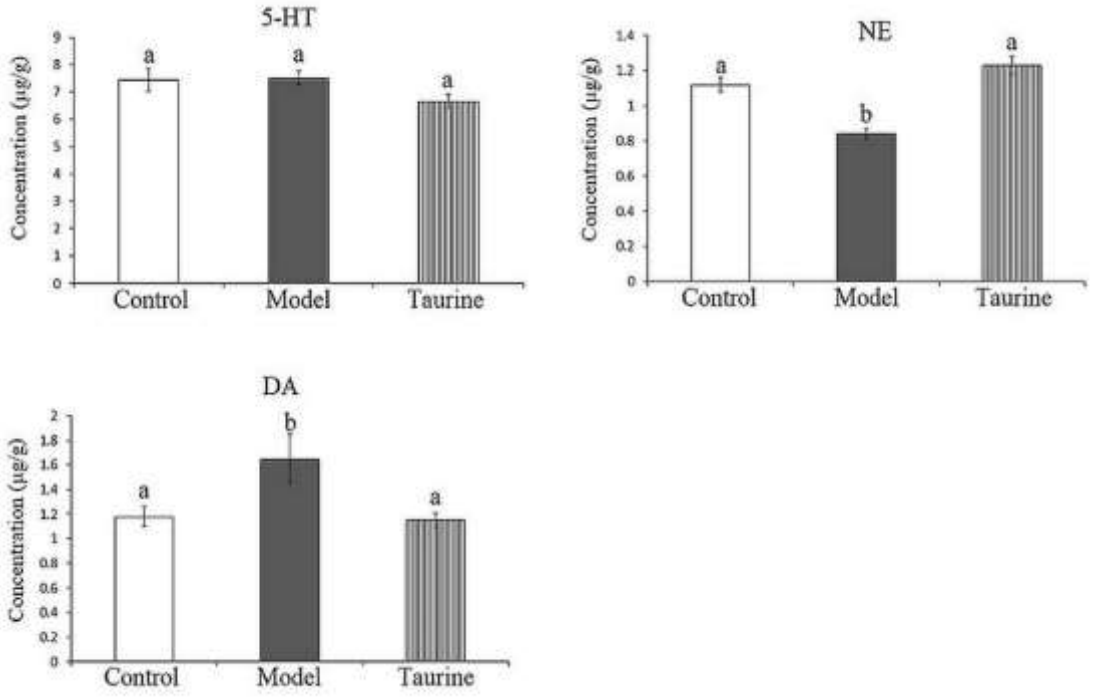

Fig.7: Effect of taurine (100 mg/kg) on the levels of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) in the cortex of rat model of dementia induced by scopolamine
Different letters indicate a significant change at P-value < 0.05 and similar letters mean nonsignificant changes between groups

Similar data were obtained in the hippocampus. 5-HT showed non-significant changes. However, NE decreased significantly by 30.69% and DA increased by 44.49% as compared to control levels. Taurine daily protection restored the changes in hippocampal levels of NE and DA to nearly control levels (Fig. 8).

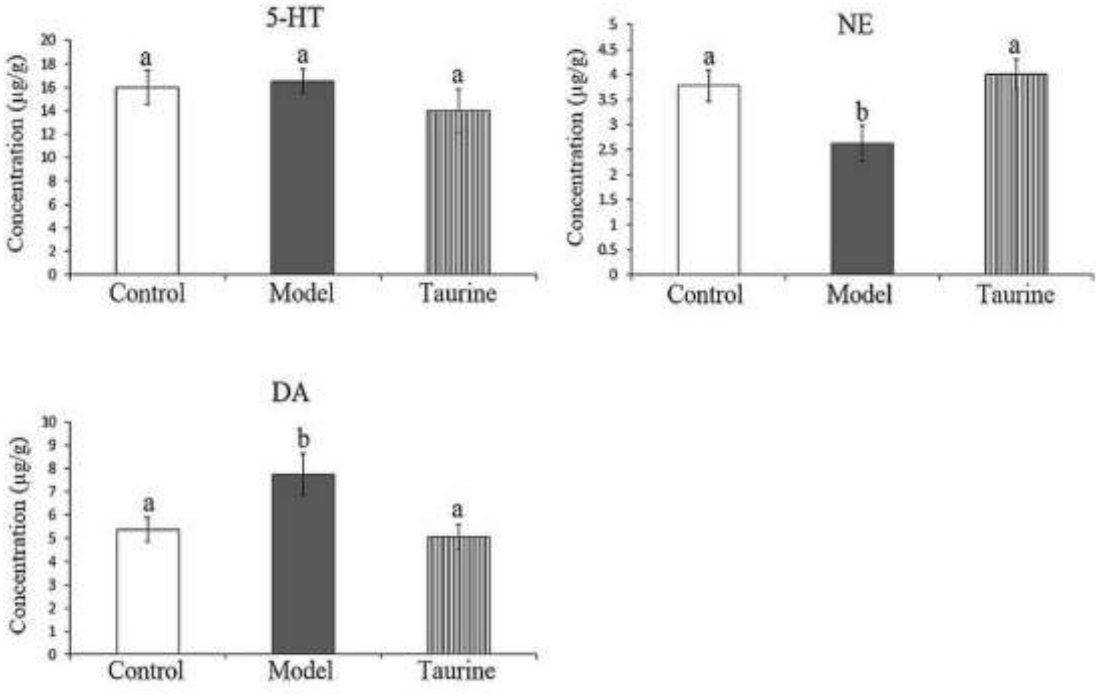

Fig.8: Effect of taurine (100 mg/kg) on the levels of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) in the hippocampus of rat model of dementia induced by scopolamine
Different letters indicate a significant change at P-value < 0.05 and similar letters mean nonsignificant changes between groups.

5. Discussion

In the current study, taurine anti-amnesic effect was investigated using scopolamine-induced rat model of dementia. Scopolamine hydrobromide easily penetrates into the brain and induces neurochemical changes that adversely affect memory and cognitive functions. Because of these effects, scopolamine is widely used to induce the rat model of dementia to evaluate the anti-amnesic effect of different agents. Previous studies have shown that systemic scopolamine administration increased cerebral oxidative stress parameters, particularly in brain regions concerned with memory and learning, as the prefrontal cortex and hippocampus [48,49].

The present findings revealed increased levels of cortical and hippocampal MDA and nitric oxide together with reduced GSH in rats treated with scopolamine. This was associated with an increase in AChE activity. The increased MDA is one of the most important indicators of the massive production of free radicals, which play a crucial role in dementia associated with ageing and neurodegenerative disease [34,50]. MDA increases as a consequence of the attack of free radicals on lipid rich organelles such as phospholipids in cell membranes and myelin. The high lipid content of the brain makes it very sensitive to oxidative stress. The production of free radicals leads to a reduction in the antioxidant stores in the brain, an effect that may explain the decreased cortical and hippocampal GSH level in the present model of dementia where GSH acts as a free radical scavenging agent.

Several studies have shown that scopolamine has a destructive effect on neurons in the cortex and hippocampus [51,52], the two brain regions involved potentially in memory and cognition. The damaging effect of scopolamine may also be attributed to the increased level of nitric oxide that interacts with the superoxide anion producing peroxynitrite. The latter compound exerts a damaging effect through protein and DNA nitration [53].

The cholinergic system has been implicated in different types of dementia, including AD, since ACh level regulates cognitive functions [10,11]. AChE is a regulatory enzyme responsible for the hydrolysis of ACh. Reducing ACh level by a critical increase in AChE activity has been found to produce deficits in learning and memory performance [3, 54]. Thus, scopolamine-induced increase in AChE activity reduces the cholinergic activity in the cortex and hippocampus by lowering ACh level, resulting in impaired memory.

Na,K,ATPase activity is a membrane-bound pump that acts to maintain the ionic gradient across the cell membrane. This pump acts by the efflux of sodium ions and the influx of potassium ions after depolarization. The present inhibition in Na+,K+,ATPase activity could be ascribed to the oxidative stress induced by scoplamine as this pump is very sensitive to free radicals [55]. The present inhibition in Na,K,ATPase activity in the cortex and hippocampus may represent one of the mechanisms responsible for the damaging effect induced by scopolamine as the inhibited Na,K,ATPase activity maintains the state of depolarization, leading to excitotoxicity and consequently neuronal death [56]. Moreover, reduced Na,K,ATPase activity produces cell death at the CNS level and also impairs learning and memory [57]. Therefore, the reduced Na,K,ATPase activity in the cortex and hippocampus may contribute to the impaired memory induced by scopolamine.

A close link between oxidative stress and inflammation is recognized, as one triggers the other [58]. Neuroinflammation mediated by increased levels of pro-inflammatory cytokines, such as TNF-, IL-1, IL-18, and IL-6, has been recorded in the brains and blood samples of patients with dementia, delirium, and postoperative cognitive dysfunction, and they have an important role in the development of neurocognitive disorders [59,60]. Scopolamine treatment was found to cause an increase in pro-inflammatory cytokines that promote inflammation [48,61]. The present study showed an increase in the neuroinflammatory markers IL-6 in the two studied brain regions and IL-1α in the hippocampus of rat model of dementia. In the CNS, IL-6 is the major inflammatory cytokine that is generated by neurons, astrocytes, microglia, and endothelial cells [62]. It acts as an important mediator of immune response and neuroinflammation [63]. The present increased IL-6 and IL-1α could be attributed to the activation of microglia, the main source of proinflammatory cytokines in the brain, by the reactive oxygen species (ROS) [64] produced by scopolamine. In brain tissue, ROS are produced by astrocytes and microglia and appear to modify synaptic and non-synaptic communication between neurons and glia, resulting in neuroinflammation and cell death, which may lead to neurodegeneration and memory loss [65]. The present increased IL-1α in the hippocampus and not in the cortex may be a region-specific effect.

The present findings showed that serotonin was not affected by scopolamine. However, norepinephrine (NE) decreased significantly in the cortex and hippocampus of rat model of dementia. Close interactions between the noradrenergic and cholinergic systems have been demonstrated. Acetylcholine has been shown to stimulate the locus coeruleus (LC), the noradrenergic neurons in rats, and this effect was reversed by scopolamine [66]. Therefore, the reduced NE level may be mediated by the inhibitory effect of scopolamine on the LC whose noradrenergic projections extend throughout the entire forebrain. In addition, the present increase in cortical and hippocampal monoamine oxidase (MAO) activity, the metabolizing enzyme of monoamines, may underlie the reduced level of NE. It has been reported that the increased activity of MAO is correlated with age, and a positive correlation exists between the brain's MAO activity and the development of AD in the transgenic mice [67,68].

Scopolamine is a muscarinic antagonist drug. Thus, it can block presynaptic muscarinic acetylcholine receptors, stimulating dopamine neurons [69]. Alterations in the interaction between dopamine and acetylcholine have been shown to be important in memory and cognition [70].

Scopolamine-induced decreases in dopamine (DA) turnover in both the hippocampus and the frontal cortex paralleled the drug-induced amnesic effects in terms of both time and dose-dependence, as measured by a passive avoidance behavioral test [71]. These findings may explain the present increase in the DA levels in the cortex and hippocampus of rat model of dementia induced by scopolamine.

It is clear from the present data that the neurochemical changes induced by scopolamine in the cortex and hippocampus underlie deficits in memory, as indicated by the novel object recognition test (NORT). This behavioral test evaluates the cognitive memory in rats depending on the native tendency of rats to recognize the novel objects [72]. The inability of rats to discriminate between familiar and novel objects means a decline in their recognition memory. The present rat model of

dementia showed a decreased value of the recognition index and a negative value of the discrimination ratio. This means that these animals spent more time at the old object and had an impaired memory as they couldn't discriminate between old and new objects.

When the rat model of dementia was treated with taurine, the rats exhibited an improvement in their cognitive memory. This was indicated by the control-like value of the recognition index and the positive value of the discrimination ratio, which indicated that rats spent more time at the novel objects in comparison to the old objects. This means that taurine-treated rats can discriminate between the novel object and the old one.

The present findings indicate that taurine treatment prevented the cortical and hippocampal oxidative stress in the rat model of dementia. This was evident from the control-like levels of MDA and NO in the two studied brain regions. The mechanisms mediating the antioxidant effect of taurine include scavenging ROS, interfering with ROS activity, regenerating thiol groups [73], and stimulating enzymatic antioxidants as superoxide dismutase [74], glutathione peroxidase and catalase [75]. In addition, as taurine is an end product of cysteine metabolism, it could maintain GSH level [76]. This in turn may explain the restored level of GSH in the cortex and hippocampus of taurine-treated rats.

The ability of taurine to prevent the increased level of NO may be due to its inhibitory effect on the inducible and neuronal nitric oxide synthases [77]. This effect precludes the formation of peroxynitrite and its severe damaging effect on the cerebral tissues.

Taurine also prevented the decline in Na,K,ATPase activity. This effect could be ascribed to taurine's antioxidant properties, which help in maintaining the integrity of the cell membrane. Therefore, preserving Na,K,ATPase activity may explain the osmoregulatory effect of taurine and could contribute to its present anti-amnesic effect by maintaining the survival of neurons.

In the present study, taurine treatment also alleviated the neuroinflammatory effect induced by scopolamine. This was indicated by the ability of taurine to reduce the increased level of Il-6 in the cortex and hippocampus. The present data agree with the findings of Nakajima et al. [78] who reported that taurine significantly decreased IL-6 levels. Thus, the present anti-inflammatory effect represents one of the mechanisms underlying the improvement in memory induced by taurine.

Another effect induced by taurine that had a crucial role in preserving cognitive memory is the restored AChE activity in the two studied brain regions. This effect helps in keeping acetylcholine level and consequently maintains normal cholinergic activity, which is strongly involved in learning and memory. The normalization of AChE activity may be induced by the antioxidant effect of taurine. Moreover, normal cholinergic activity may also help in restoring the cortical and hippocampal NE level by the stimulatory effect of acetylcholine on the noradrenergic neurons in the locus coeruleus. On the other hand, the control-like activity of MAO induced by taurine may be another factor acting to maintain NE levels in the cortex and hippocampus.

The present data showed that taurine prevented the increased level of DA exerted by scopolamine, which may be due to the ability of taurine to block the inhibitory effect of scopolamine on DA turnover. This in turn may help to attain the dopamine-acetylcholine balance in the brain, an effect that helps in the preservation of memory and cognitive function.

Evidence from preclinical and clinical studies suggests that DA and the cholinergic system act in a dynamic balance, with disturbance often resulting in psychiatric and neurological problems. Treatments for alleviating the symptoms associated with such disorders focused on restoring the balance between these two neurotransmitter systems [79].

6. Conclusion

The present behavioral and neurochemical data indicate that taurine has anti-amnesic effect against scopolamine-induced memory impairment. This effect could be attributed to its ability to prevent the cortical and hippocampal alterations in DA and NE. In addition, its potent antioxidant, and anti-inflammatory properties together with its ability to restore the activities of AChE, Na,K,ATPase and MAO may contribute of its ant-amnesic effect.

7.Conflict of interest

The authors have no conflicts of interest to declare.

8. Ethical approval

Animal procedures were performed in compliance with the recommendations of the National Institutes of Health Guide for Care and Use of Laboratory Animals (publication no. 85-23, revised 1985). All experimental procedures were strictly followed to meet the criteria of the ethical guidelines of the National Research Centre ethical committee.

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References

[1] Ritchie CW, Molinuevo JL, Truyen L, Satlin A, Van der Geyten S, Lovestone S. European Prevention of Alzheimer's Dementia (EPAD) Consortium. Development of interventions for the secondary prevention of Alzheimer's dementia: the European Prevention of Alzheimer's Dementia (EPAD) project. Lancet Psychiatry 2016; 3:179-186.

[2] Barker WW, Luis CA, Kashuba A, Luis M, Harwood DG, Loewenstein D et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the state of Florida brain Bank. Alzheimer Dis Assoc Disord 2002; 16:203–12.

[3] Puri A, Srivastava P, Pandey P, Yadav RS, Bhatt PC. Scopolamine induced behavioral and biochemical modifications and protective effect of elastrus paniculatous and Angelica glauca in rats. Int J Nutr Pharmacol Neurol Dis 2014; 4:158-69.

[4] Kalafatakis F, Bekiaridis-Moschou D, Gkioka E, Tsolaki M. Mobile phone use for 5 minutes can cause significant memory impairment in humans. Hell J Nucl Med 2017; 20 Suppl:146-154.

[5] Tanil CT, Yong MH. Mobile phones: The effect of its presence on learning and memory. PLoS One 2020; 15(8):e0219233. doi: 10.1371/journal.pone.0219233.

[6] Kim T, Kim S, Kang J, Kwon M, Lee SH. The Common Effects of Sleep Deprivation on Human Long-Term Memory and Cognitive Control Processes. Front Neurosci 2022; 16:883848. doi: 10.3389/fnins.2022.883848.

[7] Azman KF, Zakaria R, AbdAziz C, Othman Z, Al-Rahbi B. Tualang honey improves memory performance and decreases depressive-like behavior in rats exposed to loud noise stress. Noise Health 2015; 17:83-89.

[8] Tao S, Liu L, Shi L, Li X, Shen P, Xun Q, Guo X, Yu Z, Wang J. Spatial learning and memory deficits in young adult mice exposed to a brief intense noise at postnatal age. J. Otol 2015; 10: 21–28.

[9] Everitt BJ, Robbins TW. Central cholinergic systems and cognition. Annu Rev Psychol 1997; 48:649-84.

[10] Bekdash RA. The Cholinergic System, the Adrenergic System and the Neuropathology of Alzheimer's Disease. Int J Mol Sci 2021; 22(3): 1273. doi: 10.3390/ijms22031273

[11] Hampel H, Mesulam MM, Cuello AC, Farlow MR, Giacobini E, Grossberg GT et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain 2018; 141:1917-1933.

[12] Hassel B, Solyga V, Lossius A. High-affinity choline uptake and acetylcholine-metabolizing enzymes in CNS white matter. A quantitative study. Neurochem Int 2008; 53:193-198.

[13] Barnett JH, Xu K, Heron J, Goldman D, Jones PB. Cognitive effects of genetic variation in monoamine neurotransmitter systems: a population-based study of COMT, MAOA, and 5HTTLPR. Am J Med Genet B Neuropsychiatr Genet 2011; 156:158-167.

[14] Takano H. Cognitive Function and Monoamine Neurotransmission in Schizophrenia: Evidence From Positron Emission Tomography Studies. Front Psychiatry 2018; 9: 228. doi: 10.3389/fpsyt.2018.00228.

[15] Huang TT, Leu D, Zou Y. Oxidative stress and redox regulation on hippocampal-dependent cognitive functions. Arch Biochem Biophys 2015; 576:2-7.

[16] Mir RH, Shah AJ, Mohi-Ud-Din R, Potoo FH, Dar M, Jachak SM, Masoodi MH. Natural Anti-inflammatory compounds as Drug candidates in Alzheimer's disease. Curr. Med. Chem 2021; 28:4799–4825.

[17] Balschun D, Wetzel W, Del Rey A, Pitossi F, Schneider H, Zuschratter W, Besedovsky HO. Interleukin-6: a cytokine to forget. FASEB J 2004; 18:1788-90.

[18] Lyra E Silva NM, Gonçalves RA, Pascoal TA, Lima-Filho RAS, Resende EPF, et al. Pro-inflammatory interleukin-6 signaling links cognitive impairments and peripheral metabolic alterations in Alzheimer's disease. Transl Psychiatry 2021; 11(1):251. doi: 10.1038/s41398-021-01349-

[19] Murray CA, Lynch MA. Evidence that increased hippocampal expression of the cytokine interleukin-1 beta is a common trigger for age- and stress-induced impairments in long-term potentiation. J Neurosci 1998; 18: 2974-2981.

[20] Brough D, Denes A. Interleukin-1α and brain inflammation. IUBMB Life 2015; 67:323-30.

[21] Australia D., Baker S., Banerjee S. World Alzheimer Report (2019): Attitudes to Dementia. Alzheimer's Disease International; London, UK: 2019.

[22] Sharma K. Cholinesterase inhibitors as Alzheimer's therapeutics (Review). Mol Med Rep 2019; 20:1479-1487.

[23] Ruangritchankul S, Chantharit P, Srisuma S, Gray LC. Adverse Drug Reactions of Acetylcholinesterase Inhibitors in Older People Living with Dementia: A Comprehensive Literature Review. Ther Clin Risk Manag 2021; 17:927-949.

[24] Mendiola-Precoma J, Berumen LC, Padilla K, Garcia-Alcocer G. Therapies for Prevention and Treatment of Alzheimer's Disease. Biomed Res Int. 2016:2589276. doi: 10.1155/2016/2589276.

[25] Javed H, Khan A, Vaibhav K, Moshahid Khan M, Ahmad A, Ejaz Ahmad M et al. Taurine ameliorates neurobehavioral, neurochemical and immunohistochemical changes in sporadic dementia of Alzheimer's type (SDAT) caused by intracerebroventricular streptozotocin in rats. Neurol Sci 2013; 34:2181-2192.

[26] Menzie J, Pan C, Prentice H, Wu JY. Taurine and central nervous system disorders. Amino Acids 2014; 46: 31–46.

[27] Marcinkiewicz J, Kontny E. Taurine and inflammatory diseases. Amino Acids 2014; 46:7–20.

[28] Silva SP, Zago AM, Carvalho FB, Germann L, Colombo GM, Rahmeier FL et al. Neuroprotective Effect of Taurine against Cell Death, Glial Changes, and Neuronal Loss in the Cerebellum of Rats Exposed to Chronic-Recurrent Neuroinflammation Induced by LPS. J Immunol Res. 2021; 7497185. doi: 10.1155/2021/7497185.

[29] Chung MC, Malatesta P, Bosquesi PL, Yamasaki PR, Santos JL, Vizioli EO. Advances in drug design based on the amino Acid approach: taurine analogues for the treatment of CNS diseases. Pharmaceuticals (Basel) 2012; 5:1128-1146.

[30] Sun Q, Hu H, Wang W, Jin H, Feng G, Jia N. Taurine attenuates amyloid β 1-42-induced mitochondrial dysfunction by activating of SIRT1 in SK-N-SH cells. Biochem Biophys Res Commun 2014; 447:485-489.

[31] Navarro NM, Krawczyk MC, Boccia MM, Blake MG. Extinction and recovery of an avoidance memory impaired by scopolamine. Physiol Behav. 2017;171:192–8.

[32] Zhang XC, Farrell N, Haronian T, Hack J. Postoperative Anticholinergic Poisoning: Concealed Complications of a Commonly Used Medication. J Emerg Med. 2017 Oct;53(4):520-523.

[33] Ebert U, Kirch W. Scopolamine model of dementia: electroencephalogram findings and cognitive performance. Eur J Clin Invest 1998; 28:944-949.

[34] Goverdhan P, Sravanthi A, Mamatha T. Neuroprotective effects of meloxicam and selegiline in scopolamine-induced cognitive impairment and oxidative stress. Int J Alzheimers Dis. 2012:974013. doi: 10.1155/2012/974013.

[35] Han SH, Kim SJ, Yun YW, Nam SY, Lee HJ, Lee BJ. Protective effects of cultured and fermented ginseng extracts against scopolamine-induced memory loss in a mouse model. Lab Anim Res 2018; 34:37-43.

[36] Lee HL, Lim SA, Lee HW, Yoo HR, Kim HG. Yuk-Mi-Jihwang-Tang. Traditional Korean Multiple Herbal Formulae, Improves Hippocampal Memory on Scopolamine Injection-Induced Amnesia Model of C57BL/6 Mice. Evid Based Complement Alternat Med. 2018:2821040. doi: 10.1155/2018/2821040.

[37] Klinkenberg I, Blokland A. The validity of scopolamine as a pharmacological model for cognitive impairment: A review of animal behavioral studies. Neurosci. Biobehav. Rev 2010; 34:1307–1350.

[38] Liao J, Nai Y, Feng L, Chen Y, Li M, Xu H. Walnut Oil Prevents Scopolamine-Induced Memory Dysfunction in a Mouse Model. Molecules 2020; 25:1630. doi: 10.3390/molecules 25071630.

[39] Ennaceur A. One-trial object recognition in rats and mice: methodological and theoretical issues. Behav Brain Res 2010; 215:244–254.

[40] Ruiz-Larrea MB, Leal AM, Liza M, Lacort M, de Groot H. Antioxidant effects of estradiol and 2-hydroxyestradiol on iron-induced lipid peroxidation of rat liver microsomes. Steroids 1994; 59:383–388.

[41] Montgomery HAC, Dymock JF. The determination of nitrite in water. Analyst 1961; 86:414– 416.

[42] Beutler E, Duron O, Kelly OM. Improved method for the determination of blood glutathione, J. Lab. Clin. Med 1963; 61: 882–888.

[43] Tsakiris S, Angelogianni P, Schulpis KH, Behrakis P. Protective effect of l-cysteine and glutathione on rat brain Na+, K+- ATPase inhibition induced by free radicals, Z. Naturforsch 2000; 55: 271–277.

[44] Ellman GL, Courtney KD, Andres V, Featherstone RM. A new and rapid colorimetric determination of acetylcholinesterase activity, Biochem. Pharmacol 1964; 7: 88–95.

[45] Gorun V, Proinov I, Baltescu V, Balaban G, Barzu O. Modified Ellman procedure for assay of cholinesterase in crude-enzymatic preparations, Anal. Biochem 1978; 86: 324–326.

[46] Holt A, Sharman DF, Baker GB, Palcic MM A continuous spectrophotometric assay for monoamine oxidase and related enzymes in tissue homogenates. Anal Biochem 1997; 244:384-392.

[47] Ciarlone AE. Further modification of a fluoromertric method for analyzing brain amines, Microchem. J 1978; 23: 9–12.

[48] Wong-Guerra M, Jiménez-Martin J, Pardo-Andreu GL, Fonseca-Fonseca LA, Souza DO, de Assis AM, Ramirez-Sanchez J, Del Valle RM, Nuñez-Figueredo Y. Mitochondrial involvement in memory impairment induced by scopolamine in rats. Neurol Res 2017; 39:649-659.

[49] Ponne S, Kumar CR, Boopathy R. Verapamil attenuates scopolamine induced cognitive deficits by averting oxidative stress and mitochondrial injury: a potential therapeutic agent for Alzheimer's Disease. Metab. Brain Dis 2020; 35:503–515.

[50] Akter S, Hassan MR, Shahriar M, Akter N, Abbas MG, Bhuiyan MA. Cognitive impact after short-term exposure to different proton pump inhibitors: assessment using CANTAB software. Alzheimers Res Ther. 2015:79. doi: 10.1186/s13195-015-0164-8.

[51] Kim SJ, Lee JH, Chung HS, Song JH, Ha J, Bae H. Neuroprotective Effects of AMP-Activated Protein Kinase on Scopolamine Induced Memory Impairment. Korean J Physiol Pharmacol 2013; 17:331-338.

[52] Memudu AE, Adanike RP. Alpha lipoic acid reverses scopolamine-induced spatial memory loss and pyramidal cell neurodegeneration in the prefrontal cortex of Wistar rats. IBRO Neurosci Rep 2022; 13:1-8.

[53] Bartesaghi S, Radi R. Fundamentals on the biochemistry of peroxynitrite and protein tyrosine nitration. Redox Biol 2018; 14:618-625.

[54] Micheau J, Marighetto A. Acetylcholine and memory: a long, complex and chaotic but still living relationship. Behav Brain Res 2011; 221: 424-429.

[55] Mense M, Stark G, Apell HJ. Effects of free radicals on partial reactions of the Na,K-ATPase. J Membr Biol 1997; 156: 63-71.

[56] Veldhuis WB, van der Stelt M, Delmas F, Gillet B, Veldink GA, Vliegenthart JF, Nicolay K, Bär PR. In vivo excitotoxicity induced by ouabain, a Na+/K+-ATPase inhibitor. J Cereb Blood Flow Metab 2003; 23:62-74.

[57] de Lores Arnaiz GR, Ordieres MG. Brain Na(+), K(+)-ATPase Activity In Aging and Disease. Int J Biomed Sci 2014; 10:85-102.

[58] Baierle M, Nascimento SN, Moro AM, Brucker N, Freitas F, Gauer B, et al. Relationship between inflammation and oxidative stress and cognitive decline in the institutionalized elderly. Oxid Med Cell Longev. 2015: 804198. doi: 10.1155/2015/804198.

[59] Akiyama H, Arai T, Kondo H, Tanno E, Haga C, Ikeda K. Cell mediators of inflammation in the Alzheimer disease brain. Alzheimer Dis Assoc Disord 2000; 14 Suppl 1:S47-53.

[60] Simone MJ, Tan ZS. The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review. CNS Neurosci. Ther 2011; 17:506–513.

[61] Ahmad A, Ramasamy K, Jaafar SM, Majeed AB, Mani V. Total isoflavones from soybean and tempeh reversed scopolamine-induced amnesia, improved cholinergic activities and reduced neuroinflammation in brain. Food Chem Toxicol 2014; 65:120-128.

[62] Erta M, Quintana A, Hidalgo J. Interleukin-6, a major cytokine in the central nervous system. Int J Biol Sci 2012; 8:1254-1266.

[63] Kossmann T, Hans VH, Imhof HG, Stocker R, Grob P, Trentz O, Morganti-Kossmann C. Intrathecal and serum interleukin-6 and the acute-phase response in patients with severe traumatic brain injuries. Shock 1995; 4:311-317.

[64] Wang WY, Tan MS, Yu JT, Tan L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann Transl Med 2015; 3(10):136.

[65] Popa-Wagner A, Mitran S, Sivanesan S, Chang E, Buga AM. ROS and brain diseases: the good, the bad, and the ugly. Oxid Med Cell Longev 2013:963520. doi:10.1155/2013/963520.

[66] Adams LM, Foote SL. Effects of locally infused pharmacological agents on spontaneous and sensory-evoked activity of locus coeruleus neurons. Brain Res Bull 1998; 21:395-400.

[67] Kim D, Baik SH, Kang S, Cho SW, Bae J, Cha MY, Sailor MJ, Mook-Jung I, Ahn KH. Close Correlation of Monoamine Oxidase Activity with Progress of Alzheimer's Disease in Mice, Observed by in Vivo Two-Photon Imaging. ACS Cent Sci 2016; 2:967-975.

[68] Adolfsson R, Gottfries CG, Oreland L, Wiberg Å, Winblad B. Increased activity of brain and platelet monoamine oxidase in dementia of Alzheimer type Life Sci 1980; 27:1029– 1034.

[69] Roffman JL, Tanner AS, Eryilmaz H, Rodriguez-Thompson A, Silverstein NJ, Ho NF et al. Dopamine D1 signaling organizes network dynamics underlying working memory. Sci Adv 2016; 2(6):e1501672.

[70] Wisman LA, Sahin G, Maingay M, Leanza G, Kirik D. Functional convergence of dopaminergic and cholinergic input is critical for hippocampus-dependent working memory. J Neurosci 2008; 28:7797-807.

[71] Memo M, Missale C, Trivelli L, Spano PF. Acute scopolamine treatment decreases dopamine metabolism in rat hippocampus and frontal cortex. Eur J Pharmacol 1988; 149: 367-370.

[72] Cole E, Simundic A, Mossa FP, Mumby DG. Assessing object-recognition memory in rats: Pitfalls of the existent tasks and the advantages of a new test. Learn Behav 2019; 47:141-155.

[73] Jong CJ, Azuma J, Schaffer S. Mechanism underlying the antioxidant activity of taurine: prevention of mitochondrial oxidant production. Amino Acids 2012; 42:2223-2232.

[74] Wang GG, Li W, Lu XH, Zhao X, Xu L. Taurine attenuates oxidative stress and alleviates cardiac failure in type I diabetic rats. Croat Med J 2013; 54:171-179.

[75] Shivananjappa MM. Taurine attenuates maternal and embryonic oxidative stress in a streptozotocin-diabetic rat model. Reprod Biomed Online 2012; 24:558–566.

.

[76] Kim YG, Kim SK, Kwon JW, Park OJ, Kim SG, Kim YC, Lee MG. Effects of cysteine on amino acid concentrations and transsulfuration enzyme activities in rat liver with protein-calorie malnutrition. Life Sci 2003; 72:1171-1181.

[77] Askwith T, Zeng W, Eggo MC, Stevens MJ. Taurine reduces nitrosative stress and nitric oxide synthase expression in high glucose-exposed human Schwann cells. Exp Neurol 2012; 233:154-162.

[78] Nakajima Y, Osuka K, Seki Y, Gupta RC, Hara M, Takayasu M, Wakabayashi T. Taurine reduces inflammatory responses after spinal cord injury. J Neurotrauma 2010; 27: 403-410.

[79] Lester DB, Rogers TD, Blaha CD. Acetylcholine-dopamine interactions in the pathophysiology and treatment of CNS disorders. CNS Neurosci Ther 2010; 16:137-162.