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Effect of Taurine on Chronic Restraint Stress Induced Behavioural Deficits in Rodents

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Abstract
Stress is an aversive stimulus capable of altering physiological homeostasis and the ability to cope with such stressful stimuli is a crucial determinant of health and disease. Taurine (2-aminoethanesulphonic acid) constitutes about 0.1 % of body weight, it is a sulphur-containing amino acid present in virtually all cells throughout the animal kingdom. It is an important ingredient used in energy drinks. The aim of the present study is to evaluate the effects of taurine in preventing the restraint stress induced memory deficit in passive avoidance test, spatial learning, motor coordination and exploratory behaviour. Three different doses of taurine were administered (100, 200 and 400 mg/kg) to rodents subjected to chronic restraint stress (6 h/day for 21 days). The treatments were administered once daily by oral gavage. Twenty four Wistar rats were divided into four groups of six rats each also; twenty four mice were divided in to four groups of six mice each. Learning and memory in the chronic restraint-stressed Wistar rats was assessed using step down passive avoidance test, learning and memory in mice was assessed using elevated plus maze for memory, exploratory activity was assessed using hole board apparatus and motor coordination in mice was assessed using beam walk assay method. In the present study it was observed that taurine improved learning and short-time memory in chronic restraint-stressed rodents it also improved motor coordination and increased exploratory behaviour in mice.
Keywords: stress, taurine, deficit, exploratory, oral gavage, memory

Introduction

It is well known that chronic restraint stress impairs acquisition and retention of spatial memory task in rats (Sunanda *et al*., 2000). Acute and chronic stress can have both the short and long-term consequences, either protective or damaging (Seyle, 1936). Stress is an important factor of depression that causes the changes in various body systems. Research in animal health including humans have been shown to be affected by the stressful events of life inducing situation which alters cognition, learning, memory and emotional responses, resulting into mental disorders like depression and anxiety (Kondam *et al*., 2013). Long-term stress can have a detrimental effect on the body that may lead to serious disease and debilitation (Porterfield *et al*., 2011). Restraint tress is an easy and convenient method to induce both psychological (escape reaction) and physical stress (muscle work) resulting in restricted mobility and aggression (Singh *et al*., 1993). There are reports on the effects of stress on the antioxidant system and induction of lipid peroxidation in brain after restraint-induced stress model (Zaidi *et al*., 2003; Sahin and Gumuslu, 2004). There is existing report that, the balance disturbance in favour of activation of free radical processes was observed with maximal changes in the brain after restraint stress (Voronych and Iemel'ianenko 1994).

Taurine (2-amino ethanesulphonic acid), is a conditionally essential β-amino acid which is not utilized in protein synthesis. It is one of the most abundant free amino acids in mammalian tissues and is one of the three well-known sulphur-containing amino acids; the others are methionine and cysteine which are considered as the precursors for taurine synthesis. Different scientific studies emphasize on the cytoprotective properties of taurine which included anti-oxidation, anti-apoptosis, membrane stabilization, osmoregulation, and neurotransmission. Protective and therapeutic ameliorations of oxidative stress-induced pathologies were also attributed to taurine both in experimental and human models (Sirdah, 2015).

Material and Methods

Chemicals

Taurine Preparation

Taurine (CAS No. 107-35-7; purity ≥ 99%) preparation of analytical grade (100 g - Sigma-Aldrich, USA) was obtained for this study. Taurine was reconstituted as 40 % stock solution in distilled water.

Experimental animals

A total of twenty four adult Wistar rats, weighing between 150-200 g and twenty four mice weighing between 20-25 g were used in this study. The animals were obtained from the animal house of the Department of Human

Physiology Ahmadu Bello University Zaria and were assigned randomly to three treatment groups, with the experimenter blinded to the drug treatments. The animals were housed in plastic cages under normal conditions of ambient temperature in a 12 h light/dark cycle in the animal house of the Department of Human Physiology, Faculty of Medicine, Ahmadu Bello University, Zaria, Nigeria. The study was conducted in accordance with the guidelines of the National Institute of Health Guide for Care and Use of Laboratory animals (Garber *et al*., 2011). Animals were allowed free access to food and water *ad libitum*. All experiments were performed using the same timing on the day of every experiment (from 9:00 a.m. to 4:00 p.m.) during the light period.

Experimental protocol

The animals were weighed and randomly allocated into four groups, with 6 animals in each group. Group A- served as control and were given 1 ml/kg of distilled water each per os through a gavage (Akande *et al*., 2014), Group B- received 100 mg/kg of taurine per os; group C- received 200 mg/kg taurine; and group D- received 400 mg/kg taurine. The treatments were administered once daily 60 minutes prior to the commencement of the stress sessions by oral gavage for 21 days.

Chronic Restraint Stress Induction in Wistar Rats

Restraint stress was induced according to the method of (Smith, 2012) with slight modification. A perspex restraint cage with dimensions of 14 cm (L) x 5 cm (B) x 6 cm (H) was used in this experiment. Each rat was housed individually in a multi-compartment cage for the remaining time to avoid aggression and to prevent social isolation. Unrestrained rats (group A) were left undisturbed in their home cages but without access to food or water during the same period. The Wistar Rats were exposed to chronic restraint stress, 6 hour daily for 21 days (Moazzam *et al*., 2013) with slight modification by keeping them in a purpose-designed Perspex restraint cage, restraining up to 6 rats simultaneously without food and water during the restraint stress. The rats were pretreated with the various doses of taurine according to their groups 60 minutes prior to the commencement of the restraint. The stress procedure was carried out at the animal house of the Department of Human Physiology, Faculty of Medicine Ahmadu Bello University Zaria, throughout the experimental period between 9 a.m. and 4 p.m.

Chronic Restraint Stress Induction in Mice

Restraint stress was induced according to the method of (Smith, 2012) with some modification. A Perspex restraint cage with dimensions of 5 cm (L) x 3 cm (B) x 3 cm (H) was used in this experiment. Each mouse was housed individually in a multi-compartment cage for the remaining time to avoid aggression and to prevent social isolation. Unrestrained mice (control group) were left undisturbed in their home cages but without access to food or water during the same period. The mice were exposed to chronic restraint stress, 6 hour daily for 21 days (Kondam *et al*., 2013) by keeping them in a purpose-designed perspex restraint cage, restraining up to 6 mice simultaneously without food and water during the restraint stress. The mice were pretreated with the various doses of taurine according to their groups 60 minutes prior to the commencement of the restraint. The stress procedure was carried out at the animal house of the Department of Human Physiology, Ahmadu Bello University Zaria, throughout the experimental period between 9 a.m. and 4 p.m.

Learning: (Step down passive-avoidance test)

The effect of restraint stress on learning task in rats and the possible ameliorative effect of antioxidant taurine were assessed 48 hours to the termination of the study using the step-down inhibitory avoidance learning task as described by Zhu *et al*. (2001). The apparatus used for the learning test was a 40 × 25 × 25 cm acrylic chamber, consisting of a floor made of parallel 2-mm calibre stainless steel bars spaced 1cm apart. An electric shock was administered through the floor bars. A 2.5-cm-high, 8 × 25 cm wooden platform was placed on the left extreme of the chamber. Each animal was gently placed on the platform. Upon stepping down, the rat immediately received a single 80-volt foot-shock. If the animal did not return to the platform, the foot-shock was repeated every 5 seconds. A rat was considered to have learned the avoidance task, if it remained on the platform for more than 2 minutes. The number of foot-shocks applied before the animal learned the avoidance task was recorded as an index of learning acquisition.

Short-term memory:

Short-term memory was assessed in individual rat from each group using the step down avoidance inhibitory task as described by Zhu *et al*. (2001). The apparatus used for the memory test consisted of 40 × 25 × 25 cm acrylic chamber with floor made of parallel 2-mm-calibre stainless steel bars spaced 1 cm apart. A 2.5-cm-high, 8 × 25 cm wooden platform was placed on the left extreme of the chamber. In this case, the rat was again placed gently on the platform 24 hours after performing the learning task. The time an animal remained on the platform was recorded as an index of memory retention. Staying on the platform for 2 minutes was counted as maximum

memory retention (ceiling response).

Elevated plus-maze:
The elevated plus-maze was originally introduced as a model for studying anxiolytic agents. Later on, it was found that acquisition and retention processes of memory could also be studied using the elevated plus-maze. However, the parameters used for testing these two categories of agents were distinctly different. The procedure and end-point applied in the present study for testing learning and memory was as per the criteria described by the investigators working in the area of psychopharmacology and behavioral pharmacology (Itoh *et al*., 1990; Dhingra *et al*., 2003). The elevated plus maze apparatus was made up of smooth brown opaque platforms with two open arms (50 x 10 cm) and two closed arms of the same size, the wall of this chamber was 40 cm high and the whole apparatus was elevated 50 cm above the floor. On the first day, each mouse was placed at the end of an open arm, facing away from the central platform. Transfer-latency (TL) was taken as the time taken by mouse to move into one of the covered arms with all its four legs. TL was recorded on the first day. Cut-off time observed was 90 s. The mouse was allowed to explore the maze for another 10 s and then returned to its home cage. Memory retention was examined 24 h after the 1st day trial on the 2nd day.

Test for exploratory activity in mice (Hole-Board Test):
The exploratory activity of taurine in mice following oral administration was determined using the hole-board test (File and Wardil, 1975). The apparatus used consists of a brown wooden board (40 x 40cm) with four equidistant holes (1cm diameter x 2cm depth). Each mouse was placed singly at one corner of the board. It was allowed to move about and dip its head into the holes. Poking the nose into a hole is a typical behaviour of the mouse indicating a certain degree of curiosity. The number of dips in five minutes (enough time to exhibit curiosity otherwise) was recorded. The test was carried out 60 minutes after oral treatment with the taurine at the doses 100, 200 and 400 mg/kg.

Mouse beam walking assay (test for motor coordination):
This method offers improved sensitivity over the mouse Rota rod in determining motor coordination deficits induced by psychotropic agents (Stanley *et al*., 2005). Mice were allowed to walk from a start platform along a ruler (80cm long and 3cm wide) elevated 30cm above the bench by metal supports to a goal box (enclosed Hamster house). Several trials were performed for each mouse and designed such that the mice tested are aware that there was a goal box that could be reached. A ruler was used because the mouse found this easy to cross and at the same time, it induced minimum anxiety (Stanley *et al.,* 2005). Once the animals had been tested on the ruler, they were moved immediately to the beam test. The beam was made of wood, 8mm in diameter, 60cm long and elevated 30cm above the bench by a metal support. The animals were placed at one end of the beam and allowed to walk to the goal box sixty minutes after treatment with the taurine. Mice that fell were returned to the position they fell from with a maximum time of 60 seconds allowed on the beam. The number of foot slips (one or both hind limbs slipping from the beam were recorded with the aid of tally counter. The number of foot slips is a measure of motor coordination deficit. (Stanley *et al.* 2005).

Statistical analysis
Data were presented as mean ± standard error of the mean (SEM). The biochemical parameters were analyzed with one-way analysis of variance followed by Tukey's multiple comparison post-hoc test. Statistical analysis was conducted with SPSS soft ware version 20. Values of $P < 0.05$ were considered significant.

Table 1. Effect of taurine on learning and memory (Step-down avoidance test) on Wistar rats subjected to chronic restraint stress

Treatments **Taurine**	**Number of Shocks**	**Step Down Latency (sec.)**
Control (DW)	2.50±0.34	206.33±1.73
100 mg/kg	1.83±0.40	228.00±7.03
200 mg/kg	1.17±0.17	230.67±10.72
400 mg/kg	1.83±0.31	223.17±7.84

Note: values are mean ± SEM, n = 6. DW (distilled water), NS (number of shocks) and SDL (step down latency).

RESULT

The number of foot shocks (NS) was higher in the chronic restraint-stressed control groups, but this was not significant ($p > 0.05$) when compared with the taurine treated groups. In the step down latency, there were no significant ($p > 0.05$) difference when the taurine treated groups were compared with their control groups. Though the result showed that, there was increase in the SDL of the taurine groups when compared with the control group and the increase appears to be in a dose dependent manner (table 1).

Table 2. Effects of taurine on motor coordination in mice subjected to chronic restraint stress.

Treatments Taurine	Time spent on beam (sec.)	Number of foot slips
Control (DW)	50.00±4.28 [b]	10.83±0.31 [b]
100 mg/kg	40.83±5.23 [b]	08.33±1.12 [b]
200 mg/kg	36.67±5.27 [b]	07.50±0.22 [b]
400 mg/kg	10.33±2.83 [a]	04.67±0.42[a]

Note: values are mean ± SEM, n = 6. DW (distilled water)
a = b = $p < 0.05$

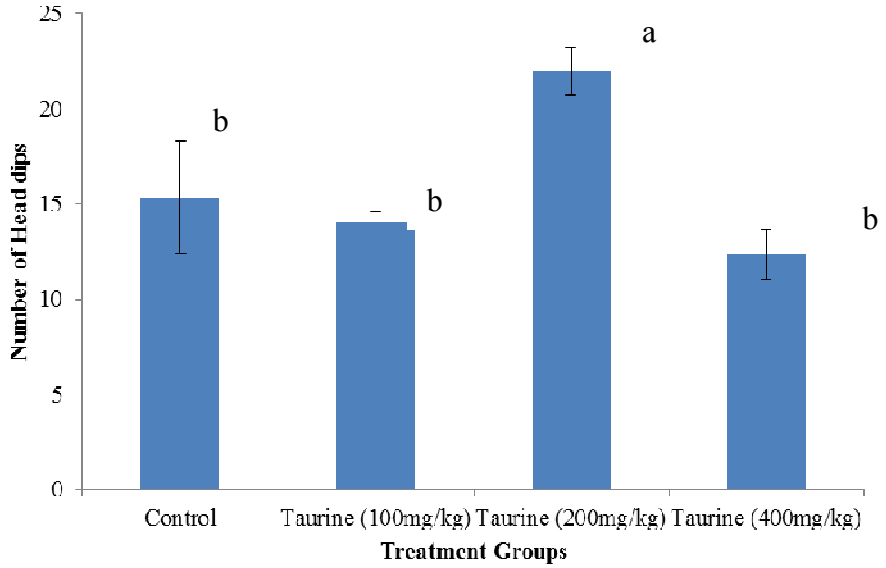
The result for the chronic restraint-stressed group showed that there was significant decrease ($p < 0.05$) in the time spent on the beam in the group administered 400 mg/kg. There was significant decrease ($p < 0.05$) in the number of foot slips in the group administered taurine 400 mg/kg when compared with the control group (table 2).

Table 3. Effects of taurine on learning and memory on mice subjected to chronic restraint stress.

Treatments Taurine	Acquisition (sec.)	Retention (sec.)
Control (DW)	77.17±8.13 [b]	47.00±10.12 [b]
100 mg/kg	71.67±12.95 [b]	22.33±2.47 [a]
200 mg/kg	54.17±7.35 [b]	22.50±7.45 [a]
400 mg/kg	47.50±12.50[a]	21.83±15.28 [a]

Note: values are mean ± SEM, n = 6, DW (distilled water)
a = b = $p < 0.05$

There was no significant ($p > 0.05$) difference when the taurine treated groups were compared with the control group. The control group showed higher acquisition values when compared with the chronic restraint-stressed control group. These higher values were seen on the first day as well as the second day (after 24 hrs) when compared with the taurine treated groups indicating taurine have improved learning and memory in the taurine treated groups (table 3).



a = b = $p < 0.05$

Figure 1. Effects of taurine on exploratory behaviour in mice subjected to chronic restraint stress

The chronic restraint-stressed groups showed significant ($p < 0.05$) increased in number of head dips in the group that received taurine 200 mg/kg. Indicating that, exploratory behaviour was more in the 200 mg/kg

group (fig.1).

Discussion

Restraint stress is a well-known method for the production of acute or chronic stress. Chronic stress may impair antioxidant defenses, leading to oxidative damage, by changing the balance between oxidant and antioxidant factors. Oxidative stress is known to play an important role in the pathogenesis of restraint-stress injury (Ganesan *et al*., 2011). Oxidative stress has been identified as a possible mechanism for the induction of cognitive impairment (Liu *et al*., 2013). Oxidative stress occurs when there is imbalance between the antioxidant defence and the production of ROS culminates in oxidative damage to biomolecules such as DNA, lipid and proteins (Halliwell and Gutteridge, 2007). The brain is very susceptible to oxidative damage because of its high oxygen content, low level of antioxidant activity and its abundant level of polyunsaturated fatty acids (Butterfield *et al*., 2001; Moreira *et al*., 2007).

In the present study, taurine treated groups showed decreased in the number of foot shock especially the group that received taurine 200 mg/kg (table 1). The taurine treated rats in all the groups spent more time on the platform in the step-down avoidance inhibitory apparatus, compared to rats in control group. This fact, apparently, showed that taurine improves cognitive functions in rats. This study agrees with the findings of Sanberg and Fibiger (1979), which found that chronic treatment with taurine, altered the impairment of acquisition and to a lesser extent, of retention of a step down passive avoidance task in rats. But the present study did not agree with the study by Rivas-Arancibia et al. (2000), which suggested that taurine did not show any effect in young and mature rats, but it was helpful in improving memory in old rats. In their study, the effect of only one taurine treatment of 43 mg/kg was determined. In a different study by Vohra and Hui (2000), taurine did not show any effect on the escape latency or the step down latency of mice. The improved learning acquisition and memory retention in the present study, was also exhibited by chronic restraint-stressed mice after taurine administration in the elevated plus-maze test as evidenced by short acquisition and retention time observed in the highest dose of taurine (400 mg/kg) in the chronic restraint-stressed group (table 3). Taurine treated mice spent less time to reach the closed arm of the elevated plus-maze as compared with the control group. Researches have shown that, taurine influences the activities of neurotransmitters in the brain and that taurine affects brain chemicals and also improves cognitive function (Sajid *et al*., 2013). Earlier studies revealed that taurine does affects learning by improving both memory acquisition and memory retention in rats (El. Idrissi, 2009). Other previous reports have indicated that, taurine administration could suppresses and also delay learning and memory abilities in rats (Ito *et al*., 2012) however there are other studies which reported no effect on learning and memory following taurine administration (Ito *et al*., 2009). In the present study it was seen that taurine improved learning and short-time memory in chronic restraint-stressed Wistar rats and mice.

Exploratory behaviour in mice revealed that, the chronic restraint-stressed group which received taurine at 200 mg/kg showed significant increased ($p < 0.05$) in the number of head dips when compared with other groups, indicating that exploratory behaviour was more in the taurine 200 mg/kg group (fig.1). Hole-board experiment is a measure of exploratory behaviour in animals (File and Wardill, 1975). A decrease in this parameter reveals a sedative behaviour while an increase indicates stimulatory activity (File and Pellow, 1985), and it has been accepted as a parameter for the evaluation of anxiety conditions in animals (Crawley, 1985). In the present study, the reason for significant decrease in the number of head dips in the taurine 400 mg/kg groups is not known however, decrease in exploratory activity by reduction in head dip is a measure of CNS depressant activity (Adzu *et al*., 2002) while an increase is a measure of CNS stimulatory activity. Hole-board model indicated that head-dipping behaviour was sensitive to changes in emotional state of the animal and suggested that the expression of an anxiolytic state in animals may be reflected by an increase in head-dipping behaviour (Tanko *et al*., 2009).This increase in exploratory behaviour of taurine at the dose of 200 mg/kg shows neuroactive property of taurine and its possible application in anxiety condition.

Taurine administration revealed significant ($p < 0.05$) decrease in the time spent on the beam in group administered taurine 200 mg/kg when compared to the control group (table 2). The time taken to reach goal-box is correlated with neuroactivity, this suggest that taurine did not exhibit sedative effect. The mouse beam walking assay used to evaluate the effect of taurine on motor coordination is a more sensitive model than rota rod in predicting clinical sedation in humans caused by novel drugs (Stanley *et al*., 2005). Taurine showed significant decrease ($p < 0.05$) in the number of foot slips in the 200 and 400 mg/kg taurine treated groups when compared to taurine 100 mg/kg. Thus suggesting that taurine does not have any depressant effect on restraint stress mice.

Conclusion

The results of the present study showed that, taurine improved learning and short-time memory in chronic restraint-stressed Wistar rats and mice. It also improved exploratory and motor coordination activities in mice subjected to chronic restraint stress. It is concluded that taurine may be a useful agent against neurobehavioural

deficit in individuals that are constantly exposed to stress.

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