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Comparative Effects of Taurine and Vitamin E in Acetaminophen-Induced Oxidative Stress on Learning and Memory in Male Wistar Rats

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Abstract: Background Stress is an integral part of human life; stressful events exert deleterious effects on normal (physiological) functions, leading to the pathogenesis of diseases. Stress alters cognition, learning, memory and emotional responses, resulting in mental disorders like depression and anxiety. The comparative effect of taurine (TAU) and vitamin E (VIT E) was evaluated on learning and memory in acetaminophen-induced oxidative stress in male Wistar rats. Methods Twenty animals weighing (100-120 g) were divided into four groups (A-D) of five rat each. Animals in Group A (control) received 0.5 ml of distilled water only while those in Group B received 100 mg/kg of acetaminophen (ACE) only. Animals in Group C received 100 mg/kg of taurine plus ACE while those in Group D received 0.5ml of Vitamin E plus ACE. The administration was done once daily for sixty days during which learning and memory of the animals were assessed using elevated plus maze and novel object recognition for rats. Results Animals in Groups A, B, C and D were able to locate the closed arm at an average of 41.0 ± 13.2 s, 67.0 ± 13.5 s, 56.3±16.6 s and 32.2± 12.1 s respectively. During the training phase, the TAU + ACE animals explored the object presented to them more (67.99 %) compared with the control and other groups. The VIT E + ACE animals have the least percentage (51.94%) in exploring the novel object that was presented to them. During the consolidation phase, the control group explored the novel object presented to them more (75.62%) when compared with the other groups. The VIT E + ACE animals have the least percentage (64.15%) in exploring the novel object that was presented to the animals. Conclusion Available evidence from this study showed that animals in acetaminophen and control groups were able to explore the elevated plus maze faster than the taurine plus acetaminophen and vitamin E plus acetaminophen groups. It also demonstrated that TAU and VIT E have protective effects on acetaminophen-associated learning and memory impairment in male rats which might be elucidated by antioxidative effects, facilitation of neurotransmitter activity and secretion of the hormone corticosterone.

Keywords: Taurine, Vitamin E, Acetaminophen, Elevated plus maze, Novel object recognition, Memory

INTRODUCTION

Stress is an integral part of human life; stressful events exert deleterious effects on normal (physiological) functions, leading to the pathogenesis of diseases arising from oxidative stress. It is described as physical and psychological modifications that disrupt the homeostasis and the balance of organisms [14]. The hypothalamic pituitary adrenocortical (APA) axis and the sympatho-adrenomedullary (SAM) system are generally considered to be the two key players in the stress response. Many diseases of modern life like hypertension, diabetes mellitus and behavioural

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disorders have been associated with deteriorated effects of stress [33].

Stress causes various changes in body systems of both animals and humans inducing situations which alter cognition, learning, memory and emotional responses, resulting in mental disorders like depression and anxiety [2]. Many negative factors exert effects on the body, which are mediated by stress-induced neurochemical and hormonal abnormalities, often associated with oxidative stress [6].

Oxidative stress is defined as an imbalance between the production of free radicals and reactive metabolites, so-called oxidants, and their elimination by protective mechanisms referred to as antioxidative systems [21]. This imbalance leads to damage of important biomolecules and organs with potential impact on the whole organism. Oxidative and antioxidative processes are associated with electron transfer influencing the redox status of cells and the organism [7].
Vitamin E is a lipid soluble antioxidant which protects the brain tissue from oxidative damage by scavenging free radicals [49]. It has been shown to have an antioxidant effect by scavenging reactive oxygen species (ROS) and inhibiting the ROS formation [13]. Vitamin E consists of two families of compounds, the tocopherols and tocotrienols, characterized by a 6-chromanol ring and an isoprenoid side chain [15]. The members of each family are designated alpha (α)-, beta (β)-, gamma (γ)-, or delta (δ)- according to the position of methyl groups attached to the chroman nucleus [4].

Acetaminophen, popularly known as paracetamol is the most common and widely used analgesic and antipyretic drug that is safe at therapeutic dosage for a wide range of treatment [45]. Its overdose is a common reason for self-poisoning worldwide resulting from its wide availability and accessibility [20]. It is fairly absorbed through the gastrointestinal tract, metabolized by glucuronidation and hydroxylation in the liver and excreted in urine [44]. Metabolites of acetaminophen lead to oxidative stress [18]. Despite its established safety profile at therapeutic doses, in overdose [43], acetaminophen is the leading cause of oxidative stress that can be fatal [37]. Although recent studies indicated the implication of cellular redox changes in acetaminophen-induced neurotoxicity [3], however, the precise mechanisms of neurotoxicity are not fully understood. In this context, it is important to search for an effective curative remedy for acetaminophen-induced oxidative damage in learning and memory.

Taurine (2-aminoethylsulfonic acid), considered a semi-essential amino acid, has several important functions, especially on the mammalian CNS acting in various processes such as osmoregulation, neuromodulation, membrane stabilization and cell proliferation [9,36]. Taurine, a sulfur-containing amino acid, is widely distributed throughout the body including the blood plasma, heart, muscle, liver and brain tissue [5]. Electrophysiological studies using rat brain preparations, however, have shown that taurine application induced long-lasting synaptic potentiation [8]. The features of the taurine-induced synaptic potentiation are similar to those of long-term potentiation, which is a typical example of synaptic plasticity and is thought to be a basic model for learning and memory [24], indicating that taurine is likely to be involved in learning and memory.

Scientific validation includes Neuwirth et al., who indicated that taurine caused varied phenotypic profiles of emotional fear learning complicated by the inability to associate cues with aversive stimuli due to potential auditory sensory overloading [35]. Ebtehal et al. showed that taurine improved undesirable Male Fertility and rat Teratogenicity induced by acetaminophen [11]. Radwan and Shehata showed that taurine and other compounds possess significant neuro- and hepato-curative attribute due to their antioxidant properties [40]. Kumari et al. reported that taurine plays multiple roles in the CNS including acting as a neuromodulator, a trophic factor in the development and as a neuroprotective agent against excitotoxicity [29]. Cai-Ling et al. saw that taurine restored the activity of acetylcholinesterase and choline acetyltransferase, which are critical for the regulation of acetylcholine [5]. Gao-Feng et al. saw that taurine possesses an anti-depressive property through regulation of the hypothalamic-pituitary-adrenal (HPA) axis and the promotion of neurogenesis, and neuronal survival and growth in the hippocampus [16]. Kim et al. stated that taurine improved cognitive impairment and may inhibit Aβ-related damages [26]. El-Idrissi suggested that taurine might help forestall the age-related decline in cognitive functions through alterations of the GABAergic system [12]. Wenting et al. saw that taurine probably has a neuroprotective effect against Aluminium-induced learning, memory and brain neurotransmitters dysfunction [46]. Ito et al. reported that peripheral administration of taurine was not involved in learning and memory [22]. Despite these studies, there is no report on the combined effect of taurine and vitamin E on learning and memory in an animal model. Therefore, this study was aimed at evaluating the comparative effect of taurine and vitamin E on learning and memory in acetaminophen-induced oxidative stressed rats.

MATERIALS AND METHODS

Equipment and Apparatus

Electronic precision balance, plastic animal cage,

sterile disposal syringe (1, 2, and 5 ml) and needles, cotton wool, stopwatch, elevated plus maze, distilled water, hand glove and methylated spirit.

Drug and Chemical Preparation

Taurine (TA) (CAS No. 107-35-7; purity ≥ 99%) preparation of analytical grade (100 g - Sigma-Aldrich, USA) was obtained commercially for this study. Taurine was reconstituted as a 40% stock solution in distilled water. Acetaminophen and Vitamin E were obtained from a store in Wukari, Nigeria and were of analytical grade. The acetaminophen (paracetamol) suspension was prepared in distilled water and animals were administered of this suspension orally using a cannula (1mL of suspension contains 0.1 g of paracetamol) (Paracetamol, Doga Drug Stock LLC, Zekeriyakoy, Istanbul, Turkey). Vitamin E was dispensed in the form of soft gelatinous capsules each containing 400 mg of dl-alpha tocopherol acetate.

Experimental Animals

Twenty (20) male Wistar rats weighing 100-120 g were used in the study. The rats were obtained from National Veterinary Research Institute (NVRI) Jos, Plateau State, Nigeria and kept in the Animal House at the Biochemistry Department, Federal University, Wukari, Taraba State, Nigeria. The animals were housed in a plastic cage measuring 16 x 12 x 10 comprising five rats per cage. All animals were allowed free access to feeds and water ad-libitum; they were maintained under standard laboratory condition that is well aerated with alternating light and dark cycle of 12 hours each at room temperature of 37.5 0C. The animals were acclimatized for two weeks prior to the commencement of the study. The experimental protocol that was approved by the Federal University Wukari Animal Ethical Review Committee was followed. All rules applying to animal safety/care were observed.

Experimental Design

The animals were divided into four groups of five animals each as follows:

Group A: Serves as the control and received 0.5 ml of distilled water only.

Group B: Received 100 mg/kg of Acetaminophen.

Group C: Received 100 mg/kg of Taurine plus 100 mg/kg of acetaminophen.

Group D: Received 0.5 ml of Vitamin E plus 100 mg/kg of acetaminophen.

All the administration of these drugs was done orally for the period of sixty days using oral cannula.

Elevated Plus Maze Protocol

The elevated plus maze was originally introduced as a model for studying anxiolytic agent. Later on, it was used in the acquisition and retention processes of memory. However, the category of agents was distinctly different in the present study for testing learning and memory as per the criteria described by the investigator working in the areas of psycho phrenology and behavioural pharmacology [10,24]. 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 rat 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 the rat to move into one of the covered arms with all its four legs. Transfer Latency was recorded on the first day and cutoff time observed was 90 s. The rat was allowed to explore the maze for another 10 s and then returned to its home cage. Memory retention was examined 24 hours after the 1st-day trials on the 2nd day.

Novel Object Recognition Task

The procedure comprised a training phase (acquisition), followed by a test phase (consolidation). In the test phase, the animal was placed in the arena, presented with two objects in the same position: one object (A1) that was used in the training phase and the other object was a novel object (B).

Training Phase: The animals were placed in the arena facing the centre of the opposite wall and exposed for a set length of time to two identical objects (A1 and A2) that are located in the corner at specified distance from each other (15 cm from each adjacent wall) and allowed to explore for 5 min. The time that the animal explored each object was measured. The rats are then removed to its home cage.

Test phase: The same was done 24 h after the training phase in order to measure long-term memory. The positions of the objects in the test and the objects used as a novel or familiar were counterbalanced between the animals. The following parameters were analyzed: the time spent exploring each object A1 and A2 in the training phase, the time spent exploring each object B and A2 (object recognition).

Data Analysis

In the elevated plus maze, data were expressed as Mean ± SEM of five determinations and were analyzed by SPSS version 20 using one-way analysis of variance (ANOVA) with multiple comparisons. Tukey's *posthoc* test was used to determine the difference between groups. Values of $p < 0.05$ were considered significant. For the novel object recognition task, data were expressed as the percentage (%) of time that the animals explored identical objects (tA2/[tA1 + tA2] x 100) during training and the % of time that the animals explored the novel object (tB/[tB+ tA2] x 100) in the retention

test (Novel Object Exploration -% Time) and total exploration time. The time percentage used for the novel object exploration was considered as an index of memory retention.

RESULTS

Effect of Taurine and VIT E on the acquisition phase of learning and memory in acetaminophen-induced oxidative stress in male Wistar rats

The result shows that during the acquisition (trial) phase, the animals in the control and ACE groups were able to explore the elevated plus maze faster than the TAU + ACE and VIT E + ACE groups. The time taken for the animals to locate the closed arm showed a significant ($p < 0.05$) decrease when compared with the animals in the TAU + ACE and VIT E + ACE groups. The time spent to locate the closed arm by animals in the TAU + ACE and VIT E + ACE groups showed a significant increase ($p < 0.05$) when compared with the control and the acetaminophen groups (Table 1).

Table 1: Effect of Taurine and VIT E on the acquisition phase of learning and memory in acetaminophen-induced oxidative stress in male Wistar rats

	(Acquisition phase in seconds)
Control	41.0 ± 13.2^{a}
ACE	32.2 ± 12.1^{a}
TAU + ACE	67.0 ± 13.5^{c}
VIT. E + ACE	56.3 ± 16.6^{b}

Values are mean ± SEM, n = 5,
ACE = Acetaminophen; **TAU** = Taurine; **VIT. E** = Vitamin E; a, b, c, d = values with different superscript differ significantly ($P < 0.05$).

Effect of Taurine and VIT E on retention phase of learning and memory in acetaminophen-induced oxidative stress in male Wistar rats

The result shows that during the retentions phase, the ACE and TAU + ACE groups took a significant ($p < 0.05$) decrease in time to locate the closed arm when compared with the control and the VIT E + ACE groups. The time spent by the control and VIT E + ACE groups showed a significant ($P < 0.05$) increase when compared with the control and the ACE and TAU + ACE groups. That is, it took the control and VIT E + ACE longer duration to locate the closed arm during the retention time (Table 2).

Table 2: Effect of Taurine and VIT E on retention phase of learning and memory in acetaminophen-induced oxidative stress male Wistar rats

	(Retention phase in seconds)
Control	28.40 ± 6.99^{a}
ACE	8.00 ± 2.07^{b}
TAU + ACE	10.20 ± 1.72^{b}
VIT. E + ACE	21.60 ± 6.88^{c}

Values are mean ± SEM, n = 5,
Ace = Acetaminophen; **Tau** = Taurine; **VIT. E** = vitamin E; a, b, c, d = values with different superscript differ significantly ($p < 0.05$)

Effect of Taurine and VIT E on object recognition in acetaminophen-induced oxidative stress in male Wistar rats (Acquisition Phase Day 1)

During the training phase, the TAU + ACE explored the object presented to them more (67.99 %) compared with control and the other groups. The VIT E + ACE have the least percentage (51.94 %) in exploring the novel object that was presented to them (Table 3).

Table 3: Effect of Taurine and VIT E on object recognition in acetaminophen-induced oxidative stress in male Wistar rats (Acquisition Phase Day 1

	Control	ACE	TAU + ACE	VIT. E + ACE
	56.82	55.00	72.41	62.96
	64.29	64.30	62.15	27.90
	56.70	74.10	47.10	60.00
	64.52	58.00	44.12	50.00
	25.60	62.10	64.10	58.82
% Average	53.59	62.70	67.99	51.94

Values are mean percentages (%), n = 5,
ACE = Acetaminophen; **TAU** = Taurine; **VIT. E** = Vitamin E

Effect of Taurine and VIT E on object recognition in acetaminophen-induced oxidative stress in male Wistar rats (Consolidation Phase Day 2)
During the consolidation phase, the control group explored the novel object presented to them more (75.62 %) when compared with the other groups. The VIT E + ACE have the least percentage (64.15 %) in exploring the novel object that was presented to them (Table 4).

Table 4: Effect of Taurine and VIT E on object recognition in acetaminophen-induced oxidative stress in male Wistar rats (Consolidation Phase Day 2)

	Control	ACE	TAU + ACE	VIT. E + ACE
	70.60	72.00	45.95	70.17
	81.50	73.81	78.80	65.90
	68.00	64.00	76.10	68.42
	78.00	73.68	74.60	61.70
	80.00	61.70	64.10	54.55
% Average	75.62	69.04	69.91	64.15

Values are mean percentages (%), n = 5,
ACE = Acetaminophen; **TAU** = Taurine; **VIT. E** = Vitamin E

DISCUSSION
The present study was aimed to investigate the potential oxidative effect of acetaminophen on the brain (learning and memory) and the possible curative effect of taurine and vitamin E.

Acetaminophen treatment induced neurochemical changes in rats in terms of increased brain levels of dopamine and norepinephrine and decreased serotonin content, thus inducing oxidative stress in the brains of the treated rats [37]. This effect might be directly due to the generation of ROS and neurochemical imbalance in the brain or learning and memory impairment. The take that acetaminophen increased both dopamine and/or epinephrine level might indicate that it enhanced the transmitters' synthesis and/or inhibited their degradation. Studies have reported that acetaminophen inhibited the enzymatic activities of monoamine oxidase and cholinesterase, but not ATPase enzyme, suggesting that acetaminophen neurotoxicity is at least partly due to neurotransmission disturbance [39,47], which is in line with this study. Also, the oxidative stress effect of acetaminophen on the brain's learning and memory ability might be due to the depleting effect of the drug on reduced glutathione [32].

In this study, taurine and acetaminophen administration in the elevated plus-maze showed improved learning and memory retention in the acetaminophen-induced oxidative stress in male Wistar rats. This agrees with the findings of Sanberg and Fibiger in 1972 and Sajid *et al.* who reported that taurine improves cognitive function [41, 42]. Taurine plus acetaminophen significantly extenuated acetaminophen-induced oxidative stress in learning and memory by reinstating the normal redox status, cognitive learning, minimizing the disturbing effect of acetaminophen on brain monoamines and alleviating acetaminophen-induced brain DNA disintegration in rats [38]. The antioxidant property of taurine plus acetaminophen may also be adduced to active cell regeneration through inhibiting the free radicals that are produced from the metabolism of toxic acetaminophen, protection of the brain and spinal nerves against free radical damage and increased synthesis of RNA and proteins [13, 17, 52]. The administration of both taurine and

acetaminophen was more efficient than the ameliorative effect of vitamin E and acetaminophen. The difference in their protective effect might be attributed to their respective antioxidant potentials [50, 51].

The highest level of recognition of the novel object by the control group after the 24 hours of drug administration (acquisition phase) suggest that the animals were able to explore the novel object more than the Wistar rats from acetaminophen group and vitamin E group owing to their high cognitive ability [34, 37]. This study agrees with the study by Gujral *et al*. with rats being subjected to a working memory test [19]. The ability of animals treated with taurine to show a high level of object recognition (69.91 %) may be adduced to improved learning acquisition and memory retention by taurine [1, 48, 49]. It may also be that taurine influenced the activities of neurotransmitters in the brain thereby improving cognitive function [31, 41]. The ability of the rats treated with vitamin E to demonstrate some level (64.15%) of object recognition may be adduced to the antioxidant potential of the compound [25, 28, 51]. The action of vitamin E may also be adduced to stress response in rats which involves the central processing of a stressor, followed by the release of corticotropin-releasing hormone (CRH) from the hypothalamus, and subsequent release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which causes the secretion of corticosterone from the adrenal cortex. Corticosterone possesses a broad spectrum of actions affecting expression and regulation of genes throughout the body preparing the organism for changes in energy and metabolism for coping with stress condition [30].

Available evidence from the elevated plus maze and novel object recognition task indicate that taurine plus acetaminophen restored neuronal function and reversed cognitive deficits induced by acetaminophen.

CONCLUSION

The results revealed that taurine and VIT E improved the impaired learning and memory ability in acetaminophen-induced oxidative stress in rats due to their antioxidant property and probably due to their ability to facilitate neurotransmitter activity and corticosterone secretion. However, these chemical messengers were not assayed in the present study.

CONFLICT OF INTEREST

Authors have not declared any conflict of interest.

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