STUDY OF OXIDATIVE STRESS PARAMETERS OF TEMPORAL CORTEX AND OPEN-FIELD ACTIVITY IN RAT EXPOSED TO ALUMINIUM AND ETHANOL IN PRESENCE OF α-TOCOPHEROL SUPPLEMENTATION

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In several attempts, supplementations with α-tocopherol have been successfully utilized to restrict or reduce the neurotoxic effects of aluminium, particularly the oxidative stress caused by aluminium. As it is already known that pro-oxidant dominance augment the neurotoxic effects of aluminium, the current study has been carried out to find whether exogenous antioxidant supplementation can lessen the aluminium-induced neurotoxicity even in pro-oxidant dominant condition. Male Wistar rats were treated with either aluminium or ethanol or both for 4 weeks along with oral α-tocopherol supplementation. All the oxidative stress parameters of temporal cortex were evaluated and found to remain undisturbed after 4 weeks of simultaneous exposure to aluminium and ethanol, except level of lipid peroxidation. Statistical evaluation of open-field activity also demonstrated no significant intra-group variation in ambulatory parameters as well explorative parameters. However, trend-line analysis against time scale demonstrated appreciable differences in some of the open-field parameters. From this study, it can be suggested that the current dose of α-tocopherol supplementation has provided some degree protection against pro-oxidant exacerbated of aluminium-induced neurotoxicity. However, studies with higher level of α-tocopherol supplementation may provide evidence of usefulness of it against neurodegeneration.

Neurotoxicity of aluminium has been proven times and again. Exposure to aluminium is inevitable. Despite of being redox-inactive metal, aluminium-induced neurotoxicity is often associated with oxidative stress. Aluminium has been already proven to be an augmenter of oxidative stress in presence of other pro-oxidants (Nayak *et al* 2010; 2012; 2014). Enhanced neurotoxic effects of aluminium and ethanol has also been demonstrated through behavioral alterations in rats (Balasai Chaitanya and Nayak, 2015; Nayak *et al* 2015) In this context, it is postulated that aluminium-induced oxidative stress might have been reduced in presence of antioxidant supplementation. Hence, there is possibility that exogenous antioxidants may prevent the aluminium-induced neurotoxicity. Being lipid soluble and naturally available, supplementation with vitamin E has been suggested as a possible approach to oppose aluminium-induced neurodegenerative changes. α-tocopherol is found to protect brain and other organs from aluminium-induced toxicity in several occasions (Halliwell and Gutteridge 1985; Pratico *et al* 2002; El-Gendy, 2011; Manal *et al* 2010; Yousef *et al* 2007; Kutlubay *et al* 2007a, 2007b, 2007c; El-Demerdash *et al* 2004; Abdel-Hamid, 2013; Abubakar *et al* 2003); however, report about failure of such protection is also available (Wang *et al* 2002).

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Temporal cortex is a known brain region to be involved in Alzheimer's disease as well as to have greater aluminium accumulation (Gupta *et al* 2005). On the other hand, iron overload has been observed in temporal cortex of aluminium-intoxicated rats (Ward et al 2001). As iron has already been implicated in aluminium-induced oxidative stress, with relatively lower reduced glutathione content (Nayak *et al* 2013) temporal cortex is one of the vulnerable regions of brain to face oxidative imbalance upon exposure to aluminium. Accordingly, massive cellular depletion is noted in temporal cortex along with other brain regions in rats which has also demonstrated significant cognitive deficiencies because of treatment with aluminium (Sarkaki *et al* 2009).

In this context, the current study is carried out to evaluate the usefulness of ?-tocopherol against aluminium-induced oxidative stress and neurobehavioral alteration, particularly in presence of other pro-oxidant (ethanol). To establish the neuroprotectant role of ?-tocopherol, biochemical parameters of oxidative stress in temporal cortex of rats have been studied along with open-field activity.

MATERIALS

Male albino Wistar rats weighing 100-120 g were procured from National Center for Laboratory Animal Sciences (NCLAS), National Institute of Nutrition, Hyderabad. All reagents used were of analytical grade and procured from Sigma, Merck, SRL, HiMedia, Loba Chemie.

METHODS

Animal maintenance and treatments

The animals were maintained with standard conditions. After one week of acclimation, rats were randomly assigned (with the help of Random Allocation Software Version 1.0, May 2004) to 4 groups (containing 5 animals in each group), namely Control group (receiving only vehicles; Al_0Et_0), Aluminium group (receiving only aluminium; Al_+Et_0), Ethanol group (receiving only ethanol; Al_0Et_+), and Aluminium-Ethanol group (receiving aluminium and ethanol both; Al_+Et_+). Animals of all the four groups were also treated orally with 5 IU of ?-tocopherol / day throughout the treatment period of 4 weeks (Nayak *et al* 2015a). Aluminium and ethanol were administered orally through orograstric gavage (maximum volume 0.2 ml) at dose of 10 mg Al (dissolved in 1% gum acacia) / Kg body weight / day and 0.6g ethanol (diluted with distilled water)/ Kg body weight / day, respectively, daily for 4 weeks (Nayak *et al* 2015a). Because of inconclusive toxicokinetic interactions of ethanol and aluminum, different treatment sessions were maintained for their exposures (Krewski *et al* 2007). Morning sessions were preferred for ethanol exposures to avoid impact of ethanol on food intake.

The experimental protocol was approved by the Institutional Animal Ethics Committee and the procedures were performed according to the guidelines of Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA, India). Body weight of each animal along with food and water intakes of each group were noted regularly.

Behavioral tests

Open-field activities of rats were recorded weekly using indigenous system (Nayak

et al 2015). A circular (diameter: 60cm), natural colored and equally illuminated (intensity of light was adjusted on the dimmer side for best result in the computerized processing) steel field had been used for the study. To perform the test, each animal was placed at the central zone with random direction and left undisturbed within the barricaded field for 10 minutes. Movements and other activities of animals were recorded with computerized video recording system. The recorded videos were converted into JPEG (Joint Photographic Experts Group) photographs with a snap at every 200ms with the help of Free Video to JPG Converter 1.8.7. Later, these photographs were processed with modified TLD© software (Tracking-Learning-Detection; kindly provided by Prof. Zdenek Kalal with GNU General Public License). The data generated further processed to identify stationary time during the experimentation (Seconds) indicating nonexplorative session(s) and time of ambulation (Seconds) indicating motor activity with exploration. The stationary time and ambulation time could be representation of anxiety because of novelty and agoraphobia. Total distance covered (Meters) and average speed of movement (Centimeters / Second) during the 10 minutes of test period indicate motor activity of the animal, while time spent at the centre (Seconds) was considered as an indicator of thigmotaxic behavior. Number of right angle turns (Counts) and wall climbing efforts (Counts) were indicators of explorative behavior of the animal confined alone in a mundane field. Time spent at first approach quadrant (Seconds), and other quadrants (Seconds; identified as right, left and opposite quadrants relative to first approach quadrant) were also noted to evaluate the nature of exploration by the animal.

Tissue collection and biochemical assays

After the period of treatment, overnight fasted rats were sacrificed by cervical dislocation. The whole brain was removed, washed with ice-cold saline and weighed immediately after soaking up the saline. Under dissection microscope, temporal cortex was separated (Chiu *et al* 2007) immediately and preserved in the ice-chamber for biochemical processing. The homogenized brain tissues were used for the determination of reduced glutathione (GSH) content, lipid peroxidation (TBARS), activities of catalase, superoxide dismutase (SOD), glutathione reductase (GR) and glutathione peroxidase (GPx) as described elsewhere (Nayak *et al* 2010). Glutathione-dependent and glutathione-independent Superoxide and peroxide handling capacities (SPHC) were calculated as described earlier (Balasai Chaitanya *et al* 2012).

Statistical analysis

Collected data were statistically analyzed using Kruskal-Wallis test for variance (KW) and the significance of the difference between groups were studied through Mann-Whitney pairwise comparison using PAST (Past 3.12© Hammer Ø, May 2016, **http://folk.uio.no/ohammer/past**) statistical package keeping probability ($p<0.05$ as cut off value.

RESULTS

The Al_+Et_+ group only have demonstrated significant reduction in body weight gain during the treatment period, while other treatment groups Al_0Et_+ and Al_+Et_0 have shown insignificant reduction in body weight gain (Table 1). However, the differences in body weight gain have not been reflected on the whole brain weight.

Table 1
Changes in body weight (g) during the treatment period and final wet weight (g) of whole brain for four groups of rats.

Body Parameters	Animal groups			
	Al_0Et_0	Al_+Et_0	Al_0Et_+	Al_+Et_+
Change in body weight (g)	70.60 ± 2.27	58.00 ± 9.10	59.80 ± 11.30	44.00 ± 6.65*
Whole brain weight (g)	1.39 ± 0.03	1.27 ± 0.05	1.35 ± 0.08	1.29 ± 0.06

Each data represents mean of five observations ± standard error of mean. * indicates significant differences with the Al_0Et_0 group.

Table 2.
Oxidative stress parameters of temporal cortex for four groups of rats.

Biochemical Parameters	Animal groups			
	Al_0Et_0	Al_+Et_0	Al_0Et_+	Al_+Et_+
Reduced glutathione (µmoles GSH / g tissue)	3.72 ± 0.11	3.53 ± 0.16	3.55 ± 0.14	3.44 ± 0.15
Lipid peroxidation (nmoles TBARS / 100 mg tissue)	12.36 ± 0.34	14.82 ± 0.90*	13.80 ± 0.98	15.16 ± 0.95*
Superoxide dismutase activity (Units / 100 mg tissue)	25.42 ± 1.10	24.76 ± 1.30	24.22 ± 1.75	23.92 ± 1.05
Catalase activity (µmoles H2O2 decomposed /hr / mg tissue)	25.92 ± 1.29	26.62 ± 1.10	27.33 ± 1.12	27.99 ± 1.44
Glutathione peroxidase activity (nmoles NADPH / min / mg tissue)	3.19 ± 0.13	3.41 ± 0.10	3.03 ± 0.26	2.80 ± 0.20
Glutathione reductase activity (nmoles NADPH / min / mg tissue)	2.17 ± 0.14	2.16 ± 0.13	2.15 ± 0.07	2.29 ± 0.09
Glutathione-independent superoxide and peroxide handling capacity	1.71 ± 0.10	1.82 ± 0.17	1.90 ± 0.09	1.95 ± 0.07
Glutathione-dependent superoxide and peroxide handling capacity	12.61 ± 0.55	14.02 ± 1.11	12.97 ± 1.76	11.69 ± 0.51

*Each data represents mean of five observations ± standard error of mean. *indicates significant differences with the Al_0Et_0 group.*

Except level of lipid peroxidation, none of the reported biochemical parameters of temporal cortex have demonstrated significant differences between the groups (Table 2). Kruskal-Wallis test revealed tie-corrected χ^2 value of 8.623 and accordingly aluminium-exposed animals, Al_+Et_0 and Al_+Et_+ groups, showed significant difference in level of lipid peroxidation of temporal cortex compared to that of the control animals, Al_0Et_0 group.

Similar to the biochemical parameters, open-field parameters like total stationary time, total distance covered, average speed and time spent at the center have not shown significant difference between the groups during all the four weeks. On the other hand,

significant differences have been noticed in weekly values of these parameters within individual group (Fig.1). All the four groups of rats have demonstrated significant tie-corrected χ^2 value in KW test for total stationary time, whereas none of the week-wise KW test has demonstrated any significant tie-corrected χ^2 value (Fig. 1A). On the other hand, in case of total distance covered (Fig. 1B), significant tie-corrected χ^2 value in KW test has been observed only in Al_+Et_0 group and only this group has demonstrated differences between weekly values. Similarly, significant tie-corrected χ^2 value in KW test has been observed in Al_+Et_0 group only, however, differences in weekly values have been observed in all the groups except Al_0Et_+ group (Fig. 1C). Even though no significant tie-corrected χ^2 value in KW test has been noted in terms of time spent at the center, first week value of Al_+Et_0 group has been found to be significantly different from that of fourth week value of same groups and first week value of Al_+Et_+ group (Fig. 1D). In terms of number of right angle turns, groups without aluminium exposure, Al_0Et_0 and Al_0Et_+ have demonstrated significant tie-corrected χ^2 value in KW test along with differences in weekly values (Fig. 1E). Fig. 1F depicts the weekly variations in spending time within different quadrants (First approach quadrant; Right, Left and Opposite quadrants in relation to first approach quadrant) for all the tested groups. Initially, animals of Al0Et0 group took more time to explore the first approach quadrant and nearby (right or left) quadrants and later they started spending more

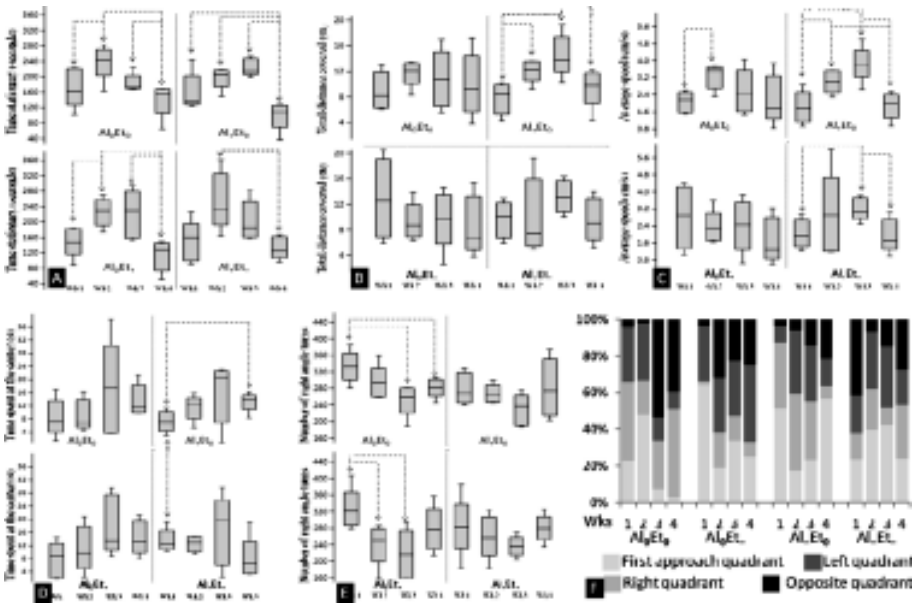

Fig. 1. Box and whisker plot of weekly values obtained from open-field activity. [A] Stationary time (seconds), [B] Total distance covered (m), [C] Average speed of movement (cm/s), [D] Time spent at the center (seconds), [E] Number of right angle turns. [F] Representation of time spent in different quadrants as 100% stacked bar. Dotted lines with arrow-heads indicate significant differences between the set of observations as per Mann-Whitney test.

time in the remote (opposite) quadrant. This pattern of exploration has also been followed by Al_0Et_+ and Al_+Et_0 group of animals, later being less explorative. However, animals of Al_+Et_+ group demonstrated slightly different pattern of exploration by spending considerable time at the opposite quadrant at the first week itself (Fig. 1F).

Second order polynomial trendlines for the behavioral parameters reported in Fig. 1 (A-E) have been depicted in Fig. 2. The trendlines demonstrate that there was no change in pattern of stationary behavior or ambulatory behavior (Fig. 2A) and number of right angle turns (Fig. 2E) with time because of aluminium or ethanol exposure. The pattern of changes of Al_0Et_+ group has been noted to be different from the other groups in terms of total distance travelled (Fig. 2B) and average speed (Fig. 2C) during the open-field activity. On the other hand, a distinct peak-shift has been observed for Al_+Et_+ group of animals in case of time spent at the center during open-field activity (Fig. 2D).

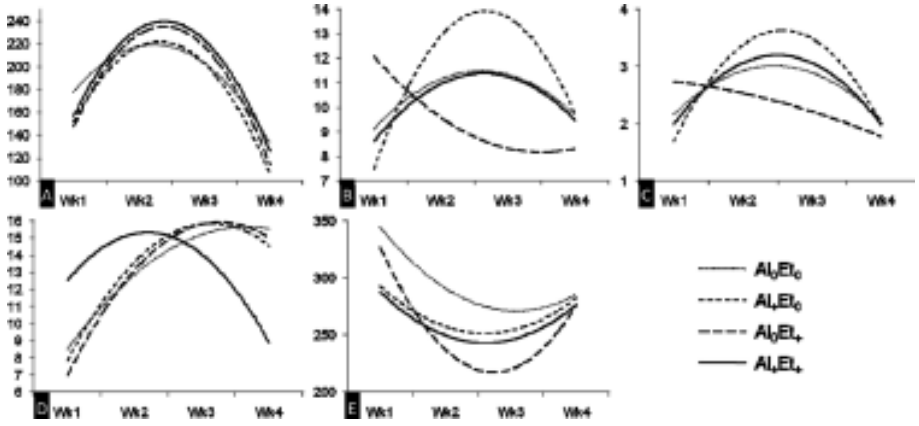

Fig. 2. Polynomial (2nd order) trendlines for weekly mean values of [A] Stationary time (seconds), [B] Total distance covered (m), [C] Average speed of movement (cm/s), [D] Time spent at the center (seconds) and [E] Number of right angle turns during the open-field activity.

DISCUSSION

In several occasions α-tocopherol has been being used as the chosen antioxidant for neuroprotection with a belief to be effective against several neurodegenerative disorders including Mild Cognitive Impairment (MCI) and Alzheimer's Dementia (AD), however, convincing evidence favoring the concept is not available (Farina *et al* 2012). Considering the obvious presence of oxidative stress during neurotoxic degeneration, supplementation of antioxidants is part of the protective and therapeutic measures.

Oxidative stress is a commonly associated phenomenon in aluminium-induced neurotoxicity. It has already been recognized that ethanol-induced prooxidant dominance allows aluminium to alter the regional SPHC and thereby augments the oxidative stress along with neurobehavioral alterations (Nayak *et al* 2013; 2014). On the other hand, Marino *et al* (2004) reviewed a number of studies reporting beneficial effects of antioxidant therapy

during ethanol exposure. Indicating protection from the inducted oxidative stress, current study does not show significant alterations in oxidative stress parameters of temporal cortex except for lipid peroxidation (Table 1) in response to concomitant aluminium and ethanol exposure to experimental rats.

Increased level of lipid peroxidation, basal as well as iron-ascorbate stimulated, has been reported in inferior temporal cortex of Alzheimer's disease (AD) patients (Chow, 2001). Similarly, Yu *et al* (2003) also noticed higher lipid peroxidation but not protein carbonylation in temporal cortex of AD patients. They have also found that the increment in lipid peroxidation was highly correlated with loss of α^4 subunit of neuronal nicotinic acetylcholine receptor (Yu *et al* 2003). This type of damage in acetylcholine receptor has been reported to be prevented by use of α-tocopherol *in vitro* (Guan *et al* 2007). Incidentally, reduced level of α-tocopherol in CSF has been observed in Alzheimer type of dementia (Chow, 2001). In kinate-induced temporal lobe epilepsy model, intraperitoneal injection of α-tocopherol has also been proven to be beneficial in improving cognitive functions of rats (Kiasalari *et al* 2016). Current study reports higher level of lipid peroxidation in temporal cortex of aluminium-exposed groups of rats. As such, temporal cortex has been reported to have unaltered oxidative stress parameters except lipid peroxidation in response to aluminium and ethanol co-exposure (Nayak *et al* 2013). Even in presence of oral supplementation of α-tocopherol, the statuses of measured oxidative stress parameters and SPHC remain same. Therefore, the dose of α-tocopherol supplementation appears to be insufficient in the current context.

Citing higher sensitivity of neurobehavioral changes compared to aluminium-induced neurochemical alterations, Sharma *et al* (2013) has proposed that evaluation of neurobehavioral parameters can help in early detection of aluminium neurotoxicity. Based on the cognitive deterioration in response to aluminium exposure to rats, aluminium-induced neurotoxicity has been recognized as an animal model for Alzheimer's disease. However, apart from cognitive impairment, decline in explorative behavior in open-field activity has been also reported in response to aluminium exposure either alone (Abdel Aal *et al* 2011) or in presence of pro-oxidant dominance (Nayak *et al* 2015). No significant difference between the tested groups in either of the reported parameters of open-field activity indicates that the reported aluminium-induced alterations in presence of ethanol co-exposure (Nayak *et al* 2015) have been nullified by the α-tocopherol supplementation in the current experiment.

Observed gradual decrease in total exploration distance (Fig. 1B and Fig. 2B) and average speed (Fig. 1C and Fig. 2C) in case of Al0Et+ group by each week of exposure may be due to improved cognitive (loss of novelty by repeated exposure to the test field) performance because of better handling of ethanol exposure and cumulative effects of continuous α-tocopherol supplementation. However, anti-anxiety and anti-agoraphobic effects of ethanol cannot be overruled especially during later weeks of exposure (Fig. 1F).

No significant difference between the tested groups is observed in terms of thigmotaxic behavior also. Significantly greater time spent at the center by Al_+Et_+ animals during first week's open-field activity compared to that of Al_+Et_0 animals (Fig. 1D) is likely to be due to slowness in movement initiation as the group has not shown any significant difference in total time of ambulation, total distance covered and average speed, while they have spent time in all the quadrants with a slightly greater share for the opposite quadrant (Fig. 1). The

peak-shift observed in the trendline of time spent at the center (Fig. 2D) also support the concept, as there was no significant difference between the weekly values in either group except significant difference between first week value and fourth week value of Al_+Et_0 group.

The current study indicates that α-tocopherol supplementation (5 IU/day) has protected the neurobehavioral alteration to some extent in male adult rats exposed to aluminium and ethanol, simultaneously. As the study is not demonstrating complete protection from oxidative stress or neurobehavioral alterations, further investigations should be carried out with higher doses of tocopherols supplementation.

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