Original Article

Oxidant handling by hippocampus and Hebb-William maze performance in aluminum-exposed albino Wistar rats

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Abstract

Background and Aim: Extensive use of aluminum in modern life made its exposure unavoidable. Hippocampus, a crucial brain structure involved in cognitive function is one of the preferred sites of aluminum accumulation. Oxidative stress was a common observation in neurodegenerative disorder (NDD) and aluminum toxicity. Therefore, the present study was planned to evaluate the association between oxidant handling capacity of hippocampus and aluminum-induced neurotoxicity.

Methods: Groups of 6 Wistar rats were administered with aluminum and concomitant exposure to different doses of pro-oxidant (ethanol) for 4 weeks. Neurobehavioral performances in Hebb-William Maze (HWM) were evaluated weekly. Oxidative stress and oxidant handling capacity of hippocampus were evaluated biochemically. Degenerative changes and deposition of aluminum in hippocampus was studied histologically. Two-way analysis of variance (ANOVA) with replication and Tukey's honest significant difference (HSD) test were performed for intergroup differences.

Results: Progressive deterioration of HWM performances was noted during the study period. Degenerative changes were boosted by aluminum and ethanol exposure but there was no indication of ethanol-induced enhancement of aluminum accumulation. No significant alteration in hippocampal oxidative stress parameter was observed upon exposure to either aluminum alone or in presence of pro-oxidant dominance.

Conclusion: The current dose and duration of aluminum exposure neither altered the oxidant status of rat hippocampus nor its oxidant handling capacity. Presence of concomitant exposure to ethanol caused decrement of superoxide and peroxide handling capacity (SPHC), in lower doses but not in higher doses, which demonstrated higher degree of degenerative changes. Therefore, the oxidative stress is not the only mechanism leading to hippocampal degeneration; in fact it might be a signaling mechanism to prevent oxidative stress faced by hippocampus.

Key words: Aluminum, Hebb-William maze, hippocampus, neuro-degeneration, oxidative stress, superoxide and peroxide handling capacity

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INTRODUCTION

Aluminum is a non-essential redox-inactive ubiquitous metal with incontrovertible neurotoxic impacts associated with oxidative stress,[1] as also seen in other biological systems.[2] Hippocampus is one of the preferred sites of aluminum accumulation.[3,4] Following chronic aluminum exposure, significant aluminum accumulation in hippocampus had been reported in hippocampus.[5] In susceptible subjects, through promotion of oxidative stress, aluminum can produce hippocampal lesions characterized by dysfunctional microtubule.[6] In addition, damaged neuritie, loss of synapse along with depletion of pyramidal cells were observed in the hippocampus of aluminum-exposed animals.[6] Shrunken cytoplasm with deeply stained eccentric nucleus along with degenerating neurons were also reported in the hippocampus of aluminum-intoxicated rats.[7] Apart from neurofibrillary degeneration and elevated amyloid precursor protein accumulation,[6] granulovacuolar degeneration had been documented in hippocampus[8] upon exposure to aluminum. While being an intermediary of neurotoxic ruination,[9] the oxidative stress is suggested as

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plausible contributing factor of the aluminum-induced cognitive impairment.[10] This notion is supported by the indispensability of hippocampus in integration of spatial memory formation.[11] Therefore, it is expected that aluminum-induced oxidative stress may lead to deterioration of hippocampal structures and finally turn into condition with compromised cognitive functions.

Living in the 'age of aluminum', exposure to aluminum is unavoidable and is continued for life time through (i) oral route by means of foods, beverages, water and medicative agents, (ii) olfactory and pulmonary routes by means of inhaling polluted air, glue sniffing in addicted individuals, (iii) transdermally along with cosmetics, ointment and sprays, and (iv) intramuscularly with vaccination and other injectables.[12] Even though, oral route provides good resistance for assimilation of consumed aluminum, it is the greatest and most common route of aluminum internalization. On the other hand, though their contribution is only nominal and mostly avoidable, the exposures to aluminum through non-enteral routes allow greater part of it to be systemized. Hepatic and renal excretion may be helpful to keep the systemic aluminum low, provided liver and kidneys are healthy.[12] Within body, though brain is not most preferred organ, aluminum gains access to brain through several mechanisms[13] but does not come out easily.[14,15] The longevity of neurons and dominance of one-way traffic of aluminum made neurons prone to intracellular aluminum accumulation.

A myriad of opportunities are there for aluminum to behave as neurotoxin,[12,13,15] the most important being the oxidative stress.[10] Noticeably, aluminum was reported to be present in 'normal' individuals[16] and the level of brain aluminum was found to be increased with normal aging.[4] A good number of experimental studies had been conducted recently to implement aluminum-induced neurodegeneration as causative factor for cognitive dysfunction, but only resulted in equivocal outcomes.[17] However, most studies confirmed the involvement of hippocampal subversion because of aluminum exposure.[3,8,10,17]

Even though the aluminum superoxide is already in the theoretical prospect,[18] presence of pre-existing oxidative stress seemed to be a pre-requisite for aluminum-associated oxidative stress in brain. In this context, concurrent exposure to ethanol and aluminum has been demonstrated to augment oxidative stress in cerebrum[19] and cerebellum.[20] Accordingly, enhancement of ethanol-induced oxidative stress was hypothesized in hippocampus while it is concurrently exposed along with aluminum. Current study was carried out to evaluate the level of oxidative stress in hippocampus and alterations in hippocampal enzymes involved in antioxidant activity. The superoxide and peroxide handling capacities of hippocampus were also appraised after the exposure to aluminum and ethanol. To impart the implication of oxidative stress on hippocampus, structural and functional studies were also carried out.

MATERIALS AND METHODS

Animal maintenance and treatments

The experimental protocol was approved by the Institutional Animal Ethics Committee. The animals were obtained, maintained and treated in the Central Animal House of the Institute and the procedures were performed according to the guidelines of Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA, India).

Male albino Wistar rats weighing 100-120 g were used in the study. The animals were maintained with standard conditions. After one week of acclimatization, rats were randomly divided (with the help of Random Allocation Software Version 1.0, May 2004) into 8 groups [Table 1] having 6 rats in each group. Both ethanol and aluminum treatments (daily for 4 weeks) were carried out through orogastric gavages. Ethanol or distilled water was given in the morning session while aluminum or vehicle was given in the evening session daily. Because of inconclusive toxicokinetic interactions of ethanol and aluminum, different treatment sessions were maintained.[21] Morning sessions were preferred for ethanol exposures to avoid impact of ethanol on food intake; while behavioral tests were carried out prior to ethanol exposure.

Table 1: Animal treatment protocol for current study

Treatment protocol			Groups of animals							
			Et-0		Et-I		Et-II		Et-III	
Timings	Treatments	Max. vol.	Al_0	Al_+	Al_0	Al_+	Al_0	Al_+	Al_0	Al_+
9 am	Ethanol (g/Kg bw)	0.2 mL	×	×	0.2	0.2	0.4	0.4	0.6	0.6
	Distilled water	0.2 mL	✓	✓	×	×	×	×	×	×
5 pm	Aluminum (10 mg/Kg bw)	0.2 mL	×	✓	×	✓	×	✓	×	✓
	Gum Acacia	0.2 mL	✓	×	✓	×	✓	×	✓	×

Alo: Animals without aluminum exposure. Al+: Animals with aluminum exposure. Et-o : Animals without ethanol exposure; Et-I: Animals exposed to 0.2 g/Kg bw ethanol; Et-II: Animals exposed to 0.4 g/Kg bw ethanol; Et-III: Animals exposed to 0.6 g ethanol/Kg bw

Tissue collection and biochemical assays

After the period of treatment, overnight fasted rats were sacrificed by cervical dislocation. The whole brain was removed, and was washed with ice-cold saline. Under dissection microscope, the hippocampi were separated 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 by Nayak P *et al*.[19]

Histological study

Formalin-fixed whole brain was carefully dissected to isolate the hippocampi of both sides. Hippocampi were stained with Einarson's chromium-gallocyanin, phloxine and fast green FCF following the protocol developed by Walton.[22]

Statistical analysis of data

The collected week-wise behavioral data and biochemical data were processed by two-way analysis of variance (ANOVA) to find out any significant impact of aluminum and ethanol exposures, as well as their interactions. The significance of differences between the groups was evaluated by Tukey's honest significant difference (HSD) test keeping α as 0.05.

RESULTS

There was no significant alteration in terms of either GSH or TBARS levels of hippocampus [Table 2] of rats that received lone aluminum exposure or varied dose of ethanol exposures or even both. Similarly, only insignificant variations were noted in terms of hippocampal catalase and GPx activities at the end of current exposure protocol. Table 2 depicted statistically significant alterations in hippocampal SOD activities (Al_+ Et-III *vs* Al_0/Al_+ Et-0) and GR activities (Al_0Et-III *vs* Al_+ Et-II) only in the highest group of ethanol exposures.

Glutathione-independent superoxide peroxide handling capacity (GI-SPHC) of hippocampus was calculated from the ratio of catalase and SOD activities of this region while ratio of GPx and SOD activities of hippocampus were used as the measure of glutathione-dependent superoxide peroxide handling capacity (GD-SPHC). Figure 1 depicted the alterations in hippocampal GI-SPHC and GD-SPHC of Al_0 and Al_+ animals from different ethanol groups. Two-way ANOVA with replication suggested significant influence of aluminum and ethanol exposures, as well as their interactions on the alterations of hippocampal GD-SPHC. Intergroup comparison of GD-SPHC demonstrated significant difference between

Table 2: Biochemical parameters of oxidative stress in hippocampus

Animal groups	GSH content (µmoles GSH/100 mg protein)		TBARS content (nmole MDA/mg protein)	
	Al_0	Al_+	Al_0	Al_+
Et-0	5.87±0.30	6.00±0.14	1.72±0.08	1.90±0.11
Et-I	5.93±0.32	5.77±0.23	1.91±0.13	1.87±0.04
Et-II	5.70±0.38	5.55±0.38	1.75±0.12	1.84±0.13
Et-III	5.93±0.18	5.14±0.27	1.82±0.09	1.64±0.05
Animal groups	**SOD activity (units/mg protein)**		**Catalase activity (µmole H_2O_2 decomposed/ hr/mg protein)**	
	Al_0	Al_+	Al_0	Al_+
Et-0	4.02±0.23	3.87±0.16	2.83±0.30	2.39±0.09
Et-I	3.97±0.17	3.88±0.12	2.42±0.12	2.38±0.23
Et-II	4.00±0.19	4.44±0.19	2.44±0.30	2.21±0.06
Et-III	4.08±0.15	3.37±0.25[a,b]	2.67±0.17	2.31±0.14
Animal groups	**GPx activity (nmoles NADPH oxidized/min/mg protein)**		**GR activity (nmoles NADPH oxidized/ min/mg protein)**	
	Al_0	Al_+	Al_0	Al_+
Et-0	32.78±2.26	35.98±2.45	32.08±4.18	36.58±1.51
Et-I	30.23±1.46	32.32±2.02	31.11±1.93	31.08±1.03
Et-II	31.18±1.01	31.05±2.07	31.95±3.39	27.21±3.43
Et-III	30.84±0.42	30.85±0.76	37.50±3.21[c]	30.33±1.82

GSH: Reduced glutathione, TBARS: Lipid peroxidation, SOD: Superoxide dismutase, GPx: Glutathione peroxidase, GR: Glutathione reductase. Al_o: Animals without aluminum exposure. Al_+: Animals with aluminum exposure. Et-o : Animals without ethanol exposure; Et-I: Animals exposed to 0.2 g ethanol/Kg body weight (bw) ; Et-II: Animals exposed to 0.4 g ethanol/Kg bw; Et-III: Animals exposed to 0.6 g ethanol/Kg bw. Each data represents mean of six observations ± SEM. [a,b,c]indicate significant differences when compared with Al_oEt-o, Al_+Et-o and Al_+Et-II, respectively

Al_0Et-0 and Al_0Et-I/III, Al_+ Et-II and Al_+ Et-0, Al_+ Et-III and Al_0Et-III, Al_+ Et-III and Al_+ Et-II. Though, GI-SPHC of hippocampus did not record any significant influence of either aluminum or ethanol exposures of current protocol, significant difference was observed between the Et-II and Et-III groups in Al_+ animals.

Figure 2 depicted the week-wise alterations in Hebb-William Maze (HWM) performances of Al_0 and Al_+ animals of different ethanol-exposure groups. Significant influence of ethanol ($P = 4.25 \times 10^{-3}$) was noticed as per two-way ANOVA with replication in the HWM performances of week 1. Only HWM performance of Al_+ animals of Et-III group was found to be significantly different from that of Al_0 animals or Et-0/II groups and Al_+ animals of Et-0 group. In week 3, performances of Al_0/Al_+ animals of Et-III group and Al_0 animals of Et-III group on HWM were found to be significantly differing from that of Al_0 and Al_+ animals of Et-0 group. The influence of ethanol was also found to be significant as per two-way ANOVA with replication in terms of HWM performances during week 3. Concomitant exposure to aluminium and ethanol caused significant influences of both aluminium and ethanol

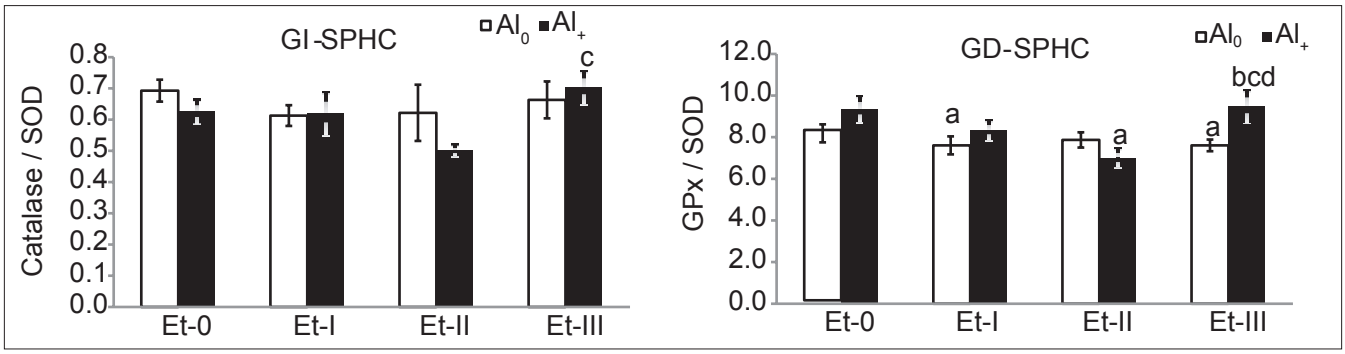

Figure 1: Glutathione-dependent superoxide and peroxide handling capacity (GD-SPHC) and Glutathione-independent superoxide and peroxide handling capacity (GI-SPHC) of hippocampus of rats of different treatment groups. Each column represents Mean ± SEM of six observations. Al0 : Animals without aluminum exposure (□). Al+ : Animals with aluminum exposure (■). Et-0: Animals without ethanol exposure; Et-I: Animals exposed to 0.2 g ethanol/Kg bw; Et-II: Animals exposed to 0.4 g ethanol/Kg bw; Et-III: Animals exposed to 0.6 g ethanol/Kg bw. Significant differences ($P < 0.05$) by HSD test are indicated by 'a' *vs* Al_+Et-0, 'b' *vs* Al_0Et-I, 'c' *vs* Al_+Et-II and 'd' *vs* Al_0Et-III

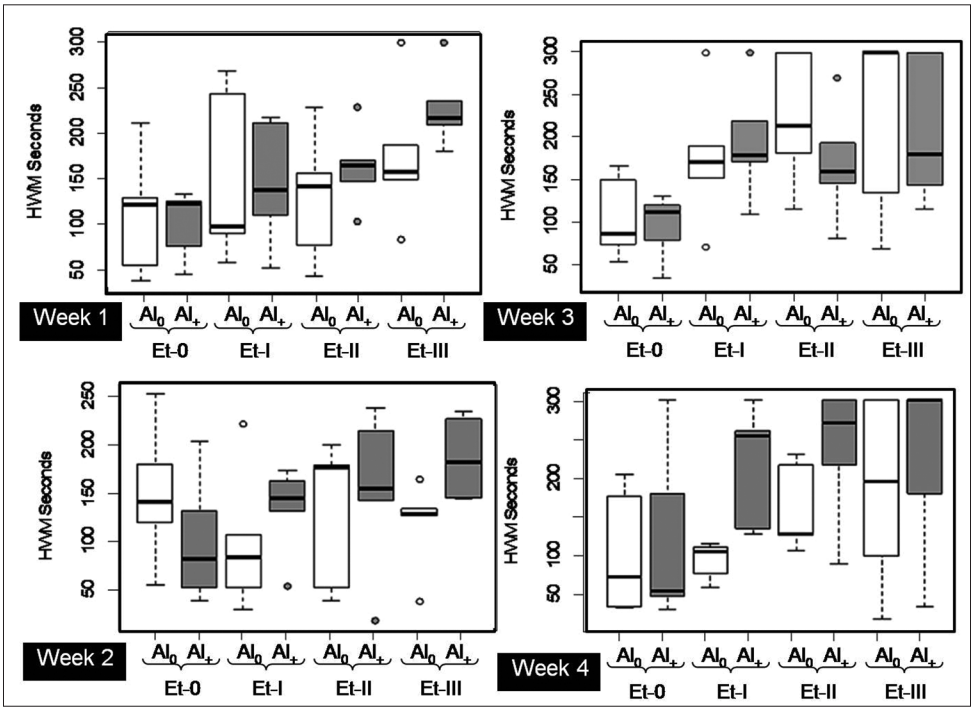

Figure 2: Week-wise box plot of Hebb-William Maze performances of different animal groups.
Al_0 : Animals without aluminum exposure, (□), Al_+: Animals with aluminum exposure (■), Et-0: Animals without ethanol exposure Et-I: Animals exposed to 0.2 g ethanol/Kg bw; Et-II: Animals exposed to 0.4 g ethanol/Kg bw; Et-III: Animals exposed to 0.6 g ethanol/Kg bw

exposures ($P = 0.01$ and 0.03, respectively, as per two-way ANOVA with replication) on the HWM performances at week 4. Intergroup comparison indicated significant differences in HWM performances between Al_+ Et-I and Al_0Et-I, Al_+ Et-II and Al_0Et-0/I, and Al_+ Et-III and Al_0Et-I.

Representative photomicrographs of hippocampus of different groups were presented in Figure 3. The CA1 region of the hippocampus had been shown with total magnification of 400× and different conditions of pyramidal cells had been indicated. Major degenerative changes were observed in both Al_0 and Al_+ animals of Et-III group. Interestingly, on the basis of appearance of nucleus, the nature of degeneration appeared to be different for Al_0 and Al_+ animals. In addition, the Al_+ animals showed distinctly higher level of aluminum deposition. Lower ethanol exposure groups indicated some degree of degenerative changes with vacuolation and karyopyknosis [Figure 3].

DISCUSSION

Cognitive impairment is a common observation in ethanol and aluminum intoxication. Chronic ethanol exposure leads to reduction in hippocampus volume which can be reversed by abstinence[23] and reduction in indigenous antioxidant status along with lowered

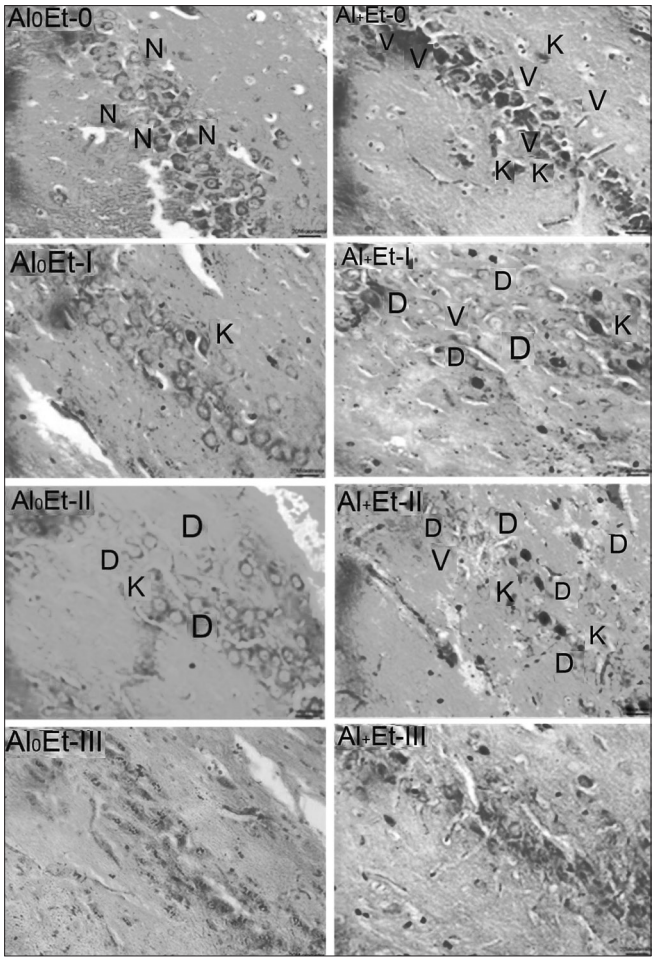

Figure 3: Representative photomicrographs (Walton staining; Total Magnification = 400X; Bar = 20 Micrometer) of hippocampus of different treatment groups of animals.

Al_0: Animals without aluminum exposure. Al_+: Animals with aluminum exposure, Et-0: Animals without ethanol exposure; Et-I: Animals exposed to 0.2 g ethanol/Kg bw; Et-II: Animals exposed to 0.4 g ethanol/Kg bw; Et-III: Animals exposed to 0.6 g ethanol/Kg bw. Pyramidal cells: Normal (N), Karyopyknosis (K), Vacuolation (V) and Degenerating (D)

antioxidant enzyme activities which can be reversed by antioxidant therapy.[24]

Progressive death of hippocampal pyramidal neurons (CA1 and CA3 regions) is feature of many neurodegenerative disorders (NDDs) and oxidative stress is one of the significant processes in the course of neurodegeneration.[25] Neuronal loss in hippocampus of Alzheimer's disease (AD) patients had been suggested to be linked with the clinical sign of memory loss in AD and CA1 region was found to be most sensitive of such neurodegeneration.[26] Even in absence of morphometric analyses, gross neurodegeneration in CA1 regions were appreciably higher in Al_+ animals of Et-I and II groups compared to respective Al_0 animals of the current study [Figure 3]. Similar aluminum-induced neurodegneration in CA1 region of hippocampus had been noted earlier.[27] On the other hand, degree of degenerations in CA1 hippocampal region of both Al_0 and Al_+ animals of Et-III group were passably similar with difference in gross cytological appearance, especially nuclear structures. Typical neuropathological changes were also observed in the hippocampus of AD model rats with oral exposure to aluminum and suggested to be associated with higher aluminum accumulation.[7] However, in absence of regional aluminum estimation its accumulation cannot be commented with certainty, as the Walton stain did not indicate remarkable higher aluminum accumulation because of concomitant exposures to ethanol along with aluminum exposure. The difference between Al_0 and Al_+ hippocampal sections were appreciable in all the Et groups, more so in Et-0 and Et-III groups. Therefore, it may be suggested that greater degenerative changes in hippocampal structures were because of the ethanol effect rather than aluminum accumulation.

Along with decreased axonal length and impaired dendritic connectivity,[28] functional impairment of CA1 neurons were also observed by suppression of long-term potentiation because of aluminum exposure and it had been linked with the poor performance in behavioral cognitive assessment.[17,29] Accordingly, HWM performances in Et-III group [Figure 2] was poor than the rest of the treatment groups even at the end of first week. On the other hand, significant influence of ethanol on the HWM performance was noted during the course of the study period, while that of aluminum was only noted on the fourth week [Figure 2]. Statistically insignificant interaction between aluminum and ethanol exposures indicated independent impacts by both the agents. Histological observations were also partially in agreement with the same. Poor cognitive performance along with degenerative changes in hippocampus was also noted in recent publications.[10,30] In terms of HWM performance, aluminum exposure alone failed to produce any negative impact even at the end of 4th week. However, with concomitant exposure to ethanol, even with very low dose of ethanol exposure (Group Et-I) significant difference was observed between the HWM performances of Al_0 and Al_+ animals. Therefore, as it has already been suggested,[17] the possibility of aluminum-induced accentuation of neurodeterioration process is emphasized by the current observations.

Significant decrease in SOD activity in hippocampus was observed after application of aluminum on the CA1 region[31] or intragastric aluminum overload.[27] However, no significant influence of either aluminum and ethanol exposures or their interaction had been noted. Rather than direct impact of aluminum on the SOD enzyme, unavailability of $O_2^{\bullet -}$, despite of excess of $O_2^{\bullet -}$ production because of aluminum exposure had been indicated as possible cause of aluminum-induced reduction of SOD activity.[31] In the current investigation also, $O_2^{\bullet -}$ may not

be available to SOD because of suggested interaction with NO[31] or aluminum itself.[18]

Aluminum exposure through intraperitoneal[32] or intragastric[6,10,27] administration or application of aluminum in the CA1 region of hippocampus[33] reported to increase the hippocampal level of lipid peroxidation. Under the current treatment protocol, aluminum exposure failed to alter the GSH and TBARS levels in the hippocampus, in the presence or absence of concomitant exposure to ethanol; while isocaloric ethanol diet could significantly enhance the TBARS level in hippocampus.[24] Therefore, the current investigation witnessed no aluminum-induced alterations in hippocampal oxidant homeostasis. Contrary to the observation of reduced activity of GPx, catalase and GR in hippocampus in response to aluminum exposure,[32] current study did not report significant alteration in either of these enzyme activities. This apparent difference was most likely due to the route of aluminum exposure; as the route of administration had been shown to influence the level of aluminum accumulation in hippocampus.[34] Thus, intraperitoneal administration of aluminum[32] was likely to have greater accumulation and eventually higher impact on the oxidant status of hippocampus compared to the oral exposure in the current study. The observations of unaltered biochemical parameter also indicated no influence of employed ethanol exposure doses on the oxidant status of hippocampus and also on the level of aluminum, as already indicated on the basis of Walton staining.

Regional redox dyshomeostasis could occur when nonpareil oxidant menace outweighs the capacity of the region to counterbalance the confronted oxidant threat. The statistically significant difference between the glutathione-independent superoxide and peroxide handling capacity (GI-SPHC) of hippocampus of Al_+ animals of Et-II and Et-III groups indicated differential responses to aluminum exposure, depending on the dose of ethanol exposure. Similarly, glutathione-dependent superoxide and peroxide handling capacity (GD-SPHC) also demonstrated significant rise in hippocampus of Al_+ Et-III animals. These alterations in SPHC could be ascribed to significant reduction in SOD activity in Al_+ Et-III animals [Figure 1].

In the present study, concomitant exposure to aluminum and ethanol caused neuropathological changes in the CA1 region of hippocampus and the impact was clearly seen in terms of HWM performances, while the oxidative stress was observed neither in terms of antioxidant enzymes activities nor in terms of SPHC. Exacerbation of oxidative stress was already reported for aluminum[19,20] while frontal cortex, but not the temporal cortex, demonstrated compromised SPHC because of concomitant exposure to aluminum and similar ethanol doses.[35] Therefore, high degree of regional specificity in terms of augmentation of oxidant imbalance could be suggested. Additionally, the present study confirms that aluminum could cause degenerative changes in hippocampus and cognitive deterioration by means other than oxidative stress.

CONCLUSION

Aluminum and ethanol are well-known neurotoxicant; in the present study they could have not only caused but also intensified each other's neurodegenerative impact on hippocampus. This real-life situation of aluminum exposure failed to initiate oxidative stress in hippocampus, even in presence of nominal to moderate pro-oxidant provocation in the form of ethanol exposure. The hippocampal damage was reflected in animal's behavioral performances, suggesting that the oxidant imbalance may not always be the postulated intercede between aluminum toxicity and neurodegeneration. However, the role of oxidative stress cannot be ruled out as it is a worsening or precipitating factor for the process of hippocampal neurodegenerative changes and eventual neurobehavioral deterioration.

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