Vet.Med.J.,Giza. Vol.53, No.2. (2005): 423-437.

EFFECTS OF CHRONIC ALUMINUM ADMINISTRATION ON BRAIN AND LIVER ENZYME ACTIVITIES AND TRACE ELEMENTS CONCENTRATION IN RATS WITH EVALUATION OF THE PROTECTIVE ROLE OF VITAMIN A AND RIBOFLAVIN

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Received: 5.3.2005.
Accepted: 15.3.2005.

SUMMARY

Aluminum (Al) has been implicated in the pathogenesis of several clinical disorders such as dialysis dementia and Alzheimer's diseases. This study investigates the effect of aluminum chloride on brain and liver function enzymes, contents of Fe, Cu, Zn, and antioxidant enzyme activities in rats and the effect of riboflavin and vitamin A in alleviating such effects. Four equal groups of Sprague Dawley rats were used (n=10).

Group1: received Al (20 mg /kg/day) for 12 weeks. Group 2: received Al and vitamin A (30 IU/g). Group 3: received Al and riboflavin (15 mg/kg). Group 4: was control. Results showed that brain function enzymes were significantly decreased in Al-treated group. Al plus vitamin A or riboflavin alleviates this reduction. Concentration of Fe was significantly decreased in cerebral and hepatic homogenates in Al and Al plus vitamin A treated groups. Concentration of Zn and Cu showed significant decrease in brain homogenates in Al treated group and non significant decrease in Al plus vitamin A or riboflavin treated groups. The activities of the antioxidant enzymes were significantly reduced in Al-treated group. Al plus vitamin A or riboflavin improved these antioxidant activities. It is concluded that Al exposure induced significant changes in the hepatic and cerebral enzymatic activities, trace elements content and antioxidant activities. The incorporation of riboflavin or vitamin A improved hepatic and cerebral functions, suggesting their protective role in aluminum toxicity.

Key words: Brain and liver enzymes, aluminum toxicity, protective role of vitamin A and riboflavin

INTRODUCTION

Aluminum (Al) is a widely distributed metal in the environment and is extensively used in modern daily life. Al enters into the body from the environment and from diet. Al-containing diet is mainly corn, yellow cheese, salt, herbs, spices, tea, and cosmetics (Yousef, 2004). Moreover, Al is incorporated in some medications such as antacids, buffered aspirins and anti-diarrheal products. Al sulfate is extensively added as a coagulant agent during the purification process of drinking water in order to folliculate the organic matter to clarify the water (Ochmanski and Barabasz, 2000).

There is no known physiological role for aluminum within the body and hence this metal may produce adverse physiological effects (Turgut et al, 2004). Elevated levels of Al in brain and bone associated with serious neurological diseases and osteodystrophic lesions have been observed in hemodialysed patients suffering from chronic renal failure due to use of dialysis solutions containing high levels of aluminum (Cannata et al, 1998). Al has been also proposed as a potential risk factor in the etiology of certain neurological disorders such as Alzheimerís disease (Yousef, 2004), amylotrophic lateral sclerosis and Parkinsonism dementia in subjects with normal renal function. This was attributed to accumulation of Al in the brain of affected individuals (Lovell et al, 1993).

Oral exposure to Al may result in accumulation of Al in hippocampus of brain and thus affect some essential elements (Zn, Fe, Cu and Ca) in the hippocampus at different degrees (Yang et al, 2002). High accumulation of aluminum in hippocampus, which could disturb the normal distribution of iron and zinc, decrease the activities of antioxidant enzymes and increase the level of lipid peroxidation, which may lead to the neurotoxicity of aluminum (Domingo et al. 1993; Jia et al, 2001). Moreover, Al can bind to DNA or RNA molecules and thereby inhibiting the activity of some enzymes, such as hexokinase, acid and alkaline phosphatases, phosphooxydase and phosphodiestrase (Ochmanski and Barabasz, 2000).

A number of studies demonstrated that supplementation with some vitamins and trace elements may reduce or protect against the harmful effects of aluminum in different animal species. Ascorbic acid (vitamin C), being antioxidant, ameliorated the adverse effect of aluminum administration in rabbits, by decreasing the free radicals, cholesterol, creatinine, and increasing the activity of GST (Yousef, 2004). Vitamin E and selenium has been found to negate the toxic effects of Al in rats (El-Demerdash, 2004). However, the role of vitamin A and riboflavin in ameliorating the toxic effect

of Al has not been investigated in rats.

Considering the widespread presence of aluminum in the environment and the susceptibility of the brain and liver to peroxidative damage; the aim of this study was to:

1) Investigate the effects of chronic Al exposure on rat brain and liver content of Fe, Zn and Cu, lipid peroxidation and antioxidant enzymes activities as well as the serum hepatic and brain function enzymes.
2) Investigate the efficacy of vitamin A and vitamin B2 (riboflavin) in alleviating the toxic effects of Al.

MATERIALS AND METHODS

Animals and Experimental Design

This study was performed on forty adult male albino Sprague Dawley rats weighing between 150-180 g. The Animals were housed in stainless steel cages and maintained on suitable hygienic conditions. Rats were allowed for acclimatization for 12 days prior to experimentation. Water was offered ad libitum. Rats were randomly divided into four equal groups, each of ten rats. The first group received aluminum chloride ($AlCl_3$) (Sigma) as previously described (Sarin et al, 1997) with minor modification. Al was given orally at a dose of 20 mg /kg body weight/day dissolved in bi-distilled water for 12 weeks. The second group received the same Al dose together with diet enriched with vitamin A (30 IU /g) as retinyl acetate (five times the content of vitamin A in the control group) according to (Sato and Lieber 1981). The third group received the same Al dose with riboflavin in a dose of 15 mg/kg body weight orally (Satanovskaya and Sadovnik 1990). The fourth group served as control, and fed a well-balanced laboratory rat diet.

Blood Sampling and Sera Collection

The blood samples were collected by heart puncture before the animals were sacrificed by cervical dislocation. Sera were separated and used freshly for determinations of the liver and brain enzyme activities.

Preparation of Homogenates

After the end of experimental period, rats were fasted overnight with free access for water and then scarified under diethyl ether anesthesia (Reis et al, 1994). Liver and brain tissue samples were quickly dissected, rinsed in ice-cold saline to clear them of blood. About one gram of the liver and brain were homogenated immediately with 9.00 ml potassium phosphates buffer solution pH 7.40, then briefly solicited and centrifuged at 3000 rpm for 15 min. the supernatant was separated and used freshly for biochemical assays.

Determination of Fe, Zn and Cu concentrations

Fe, Zn and Cu were determined in liver and brain homogenates using Pirkin Elmer Model 23000 Atomic Absorption Spectrophotometer (in faculty

of science, Alexandria University) according to Watanabe (1996). The concentrations were measured as µg/g tissue.

Determination of Lipid Peroxidation

Lipid peroxides in both liver and brain homogenates were ascertained by measuring malondialdehyde (MDA) by thiobarbituric acid method (Uchiyama and Mihar, 1976). MDA was measured as nmol/mg protein.

Determination of Antioxidant Enzymes

The activities of GSH-Px, GR-ase, t-SOD and Catalase were determined according to the methods of Chiu et al, (1976), Bergmayer, (1983), Misra and Fridovich, (1972), and Sinha, (1972), respectively.

Determination of Liver Enzymatic Activities

The activity of gamma glutamyl transferase (GGT) was determined in liver homogenate as previously described (Persijn and Van, 1976). The activities of alanine amino transferase (ALT), asparate amino transferase (AST) and alkaline phosphatase (ALP) were determined by the method described by Belifield and Goldburg, (1971).

Determination of Brain Enzymatic Activities

The activity of Monoaminooxidase (MAO), acetylcholinestrse (AChE), and 5'-nucleotidase (5'-NT) were determined by the methods of Mc Eween, (1969), Den Blaauwen et al, (1983), Bertrand and Buret, (1982).

Statistical Analysis

Data were expressed as mean ± SE. Differences between groups were examined for statistical significance using the Studentís t- test as explained by Petrie and Waston (1999). All differences were considered as statistically different at $P < 0.05$.

RESULTS

1- Changes in Fe, Zn and Cu Concentrations in Liver and Brain Homogenates:

The effect of Al on trace elements concentrations in liver and brain tissues either alone or in combination with vitamin A or riboflavin is described in figure 1. Administration of Al for 12 weeks resulted in significant ($P<0.05$) decrease of iron concentration in both liver and brain tissues; whereas Al plus vitamin A showed significant ($P< 0.05$) decrease of iron in liver tissue and non significant decrease in brain tissue. Combination of Al and riboflavin resulted in a non-significant decrease of iron concentration in both liver and brain tissues.

Zn concentration showed significant increase in liver tissues of all treated groups; whereas the brain showed significant decrease in Al-treated group and non-significant increase in Al plus vitamin A or riboflavin groups.

Non-significant decrease was recorded in the concentration of Cu in liver and brain tissues of Al-treated groups. Al plus vitamin A or riboflavin treated groups showed non-significant increase in Cu concentration in liver tissue and non-significant decrease in brain tissue.

2- Changes in Lipid Peroxides and Glutathione Redox Cycle:

In liver homogenate, Al-treated group showed significant increase ($P<0.05$) in the activity of GSH-px, non significant increase in the activity of GR-ase and significant decrease in the activity of catalase and t-SOD. The combination of vitamin A with Al significantly elevates ($P < 0.05$) the activity of catalase; while the incorporation of riboflavin significantly increased ($P < 0.05$) both catalase and GR-ase compared to Al-treated group.

A Significant increase ($P < 0.05$) in lipid peroxides, represented by MDA (an index of lipid peroxidation) in the brain tissue of Al-treated groups compared to control was recorded. The MDA was significantly reduced ($P < 0.05$) in groups treated with Al plus vitamin A compared to Al-treated group. In the liver tissue there was a significant increase ($P < 0.05$) in lipid peroxide concentration in Al treated group compared to control; while in Al plus vitamin A or riboflavin there was a significant decrease compared to Al-treated group (Table 1).

Al-treated group showed significant decrease ($P < 0.05$) in the activity of GSH-Px, catalase, t-SOD and non significant decrease in the activity of GR-ase in the brain tissue. Groups treated with Al plus vitamin A or riboflavin revealed significant increases in the activity of GSH-Px and t-SOD in brain tissue homogenate (Table1).

3- Changes in Serum Hepatic and Brain Function Enzymes:

The results of the changes in the serum parameters including, hepatic and brain function enzymes are described in Table 2.

Al-treated group showed a significant ($P < 0.05$) increase in the activities of ALT, AST, GGT and ALP compared to control. Al plus vitamin A or riboflavin treated groups showed a significant reduction ($P < 0.05$) in the activity of ALT, AST, GGT and ALP compared to Al-treated group (Table 2).

A significant decrease ($P < 0.05$) in the activities of MAO, AChE, and 5'-NT in Al-treated group compared to control was found. The combination of either vitamin A or riboflavin with Al significantly elevates ($P < 0.05$) the activities of MAO, AChE, and 5'-NT compared to group exposed to Al alone.

Table 1: Changes of hepatic and brain MDA, GSH-Px, catalase, t-SOD and GR-ase in control and experimental groups. Results are shown as means ± SE (N = 10). Vit A is vitamin A. Ribo is riboflavin.

	Liver				Brain			
	Control	Al	Al + Vit A	Al + Ribo.	Control	Al	Al + Vit A	Al + Ribo.
MDA (nmol/mg protein)	1.51 ± 0.05	5.48 ± 0.25[a]	0.79 ± 0.04[b]	1.05 ± 0.06[b]	0.46 ± 0.04	1.20 ± 0.08[a]	0.99 ± 0.07[b]	0.96 ± 0.06
GSH-Px (U/g protein)	445.40 ± 4.88	505.80 ± 4.01[a]	491.10 ± 6.86	493.9 ± 5.64	15.99 ± 0.54	11.90 ± 0.52[a]	14.80 ± 0.55[b]	13.55 ± 0.65[b]
Catalase (U/g protein)	29.90 ± 1.15	15.70 ± 0.42[a]	19.90 ± 0.67b	21.30 ± 0.79[b]	3.62 ± 0.36	1.84 ± 0.19[a]	2.48 ± 0.24	2.68 ± 0.20[b]
t-SOD (U/g protein)	8.84 ± 0.28	7.47 ± 0.41[a]	8.53 ± 0.29	7.93 ± 0.38	6.64 ± 0.24	2.63 ± 0.18[a]	4.59 ± 0.25[b]	6.07 ± 0.34[b]
GR-ase (U/g protein)	49.60 ± 2.19	52.70 ± 2.51	46.40 ± 2.02	42.20 ± 2.73[b]	18.04 ± 0.48	17.02 ± 0.52	16.92 ± 0.67	17.86 ± 0.55

[a] Significant difference from control at P < 0.05.

[b] significant different from Al-treated group at P < 0.05.

Table 2: Changes of some hepatic and brain function enzymes in control and experimental groups. Results are shown as means ± SE N = 10.

	Liver function enzymes				Brain functions enzymes				
	Control	Al	Al + Vit A	Al + Ribo.		Control	Al	Al + Vit A	Al + Ribo.
ALT (U/L)	44.20 ± 2.12	137.20 ± 1.63[a]	115.80 ± 1.64[b]	101.30 ± 1.80[b]	MAO U/ml	23.00 ± 0.52	9.10 ± 0.43[a]	12.80 ± 0.53[b] 4.81	18.85 ± 0.46[b]
AST (U/L)	152.60 ± 2.03	196.60 ± 2.27[a]	176.30 ± 1.80[b]	181.50 ± 2.37[b]	AChE U/ml	6.44 ± 0.45	2.28 ± 0.29[a]	± 0.32[b]	4.87 ± 0.35[b]
GGT *U/L)	1.70 ± 0.07	6.39 ± 0.13[a]	1.53 ± 0.09[b]	1.87 ± 0.14[b]	5'-NT U/ml	4.95 ± 0.36	2.26 ± 0.44[a]	3.67 ± 0.37[b]	3.59 ± 0.31[b]
ALP (U/L)	18.65 ± 0.78	54.00 ± 1.94[a]	25.30 ± 1.24[b]	27.80 ± 0.71[b]					

[a] Significant difference from control at P < 0.05.

[b] significant different from Al-treated group at P < 0.05.

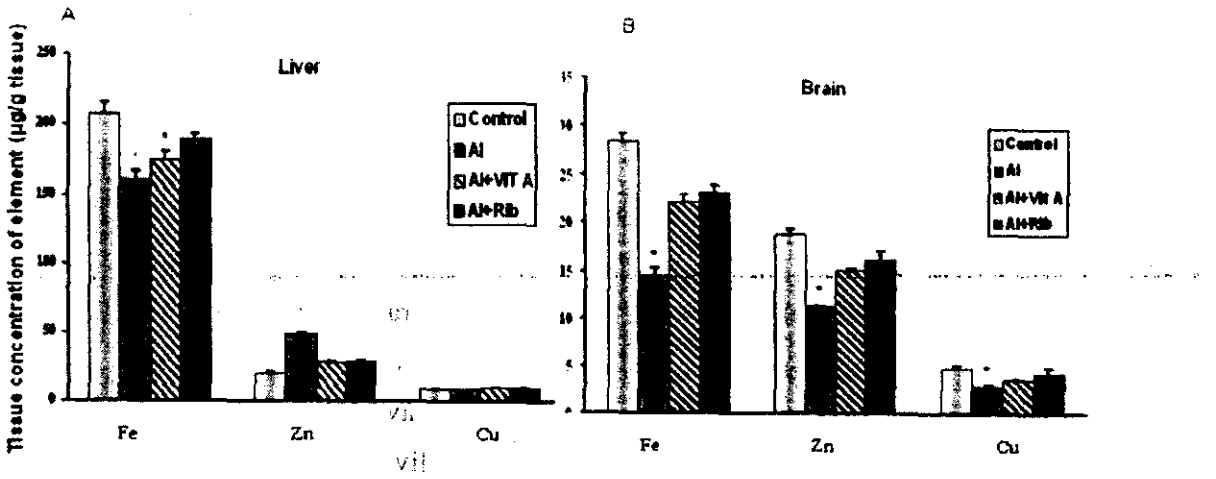

Figure 1: Changes in Fe, Zn and Cu concentrations in liver and brain tissues homogenates. (A) In liver, Fe concentration is significantly decreased in rats received Al and rats received Al plus Vitamin A compared to control. Cu concentration is significantly higher only in rats received Al compared to control. Zn concentration is not significantly affected. (B) In brain, Fe, Cu and Zn concentrations are significantly decreased in rats received Al compared to control and non-significantly affected when Al combined with vitamin A or riboflavin. Results are shown as mean ± SE N = 10.* indicate significant difference from control group at $P < 0.05$.

DISCUSSION

The role of heavy metals in the pathogenesis of neurodegenerative disease is currently receiving considerable attention. Aluminum is present in many manufactured foods and medicines and is added to drinking water for purification purposes. It has been proposed that aluminum is a contributing factor to several neurodegenerative disorders such as Alzheimer's disease. However, this remains controversial primarily due to the unusual properties of aluminum and a lack of information on its cellular sites of action (Levesque et al, 2002). Presence of aluminum in dialysis fluids has been shown to be an etiological factor contributing to several neurological disorders known as dialysis dementia (Nayak and Chatterjee, 2003).

Fe and Al are carried mainly by transferrin and chelated by the same compounds (desferrioxamine) and both may compete for absorption and cellular uptake. The decrease in liver and brain Fe in the present study (Fig. 1) may be attributed to the competition of Al with Fe to be transported from the intestine via transferrin. This result agrees with the data obtained by (Deloncle et al, 2001) who demonstrated that the radio-labeled iron absorption was significantly reduced in rats with Al intoxication and also in intestinal cells previously incubated with Al. Moreover, Al af-

fects iron homeostasis by interfering with iron regulatory proteins (Ward et al, 2001). The reduction in Fe concentration was also demonstrated in cortex homogenate of rat exposed to intraperitoneal injection of aluminum (Esparza et al, 2003).

In brain homogenate, the Cu and Zn contents were significantly decreased in Al-treated group compared to control. This result agrees with Yang et al, (2002) who recorded a reduction of Fe, Cu and Zn content in hippocampus of brain after oral exposure to Al. Significant reduction of Cu and non-significant reduction of Zn were also reported in cortex and hippocampus of rats with Al intoxication induced by intraperitoneal injection of aluminum (Esparza et al, 2003). Accumulation of aluminum and the accompanying reduction of iron, copper and zinc in brain might interpret the neurotoxicity of aluminum. Iron is an essential element that ensures brain oxygenation, to produce energy in the cerebral parenchyma, and for the synthesis of neurotransmitters (Bourre, 2004). It has been demonstrated that zinc supplementation as zinc-histidine protects cultured neurons against oxidative insults and inhibits apoptosis and therefore; zinc, in the form of zinc-histidine, is recommended for the treatment of diseases of the CNS associated with zinc deficiency (Williams et al, 2004). Cu is a component of the antioxidant enzyme superoxide dismutase (SOD), which is one of the major enzymes by which cells overcome the deleterious effects of reactive oxygen species (Sik Eum et al, 2004). Therefore reduction of Cu concentration by Al toxicity may increase the oxidative stress.

The combination of vitamin A or riboflavin produced non-significant changes in Cu and Zn concentrations in liver and brain compared to control. Therefore, the incorporation of vitamin A or riboflavin ameliorated the effect of Al on Zn and Cu concentrations in rat brain. The combination of Al with riboflavin ameliorated the effect of Al on iron in both liver and brain and produced non-significant changes compared to control. This may be attributed to the important role of riboflavin in the absorption, metabolism and utilization of iron (Lynch, 1997). The combination of vitamin ameliorated the Fe-mediated reduction in brain tissue only as the Fe concentration was not significantly affected by Al combined with vitamin A. Consistent with that, vitamin A helps in iron transport, hemoglobin production and thus improves the status of iron stores (Singh, 2004).

In liver homogenate, there was a significant increase in Zn concentrations compared to control. The combination of Al with either vitamin A or riboflavin reduced the Zn concentration. On the other hand, Cu concentration was not significantly affected by Al treatment, a finding that is consistent with that reported by Esparza et al, (2003). Therefore, the Cu was not affected in liver but significantly decreased in brain following Al exposure. This result suggests that Cu level in brain is highly sensitive to aluminum toxicity but less sensitive in liver, presumably because most of the absorbed Cu enters the portal circulation

where it is bound to carrier proteins (primarily albumin), peptides and amino acids and is transported to the liver (Harris, 1991), with lesser amounts entering the kidney (Linder and Hazegh-Azam, 1996).

Peroxidation of proteins and nucleic acids has been related to a number of pathophysiological and neurological situations of brain. Aluminum salts has been shown to accelerate the iron-induced peroxidation of brain phospholipid liposomes (Oteiza, 1993). The end products of lipid peroxidation are often highly cytotoxic. The brain is the organ most susceptible to peroxidative damage (Julka and Gil, 1996). The increase in lipid peroxides recorded in this study (Table 1) is most related to the ability of Al to augment lipid peroxidation by enhancing the production of reactive oxygen intermediates. This result is supported by the reported data of Moyer (1999) who suggested that the diseases of the central nervous system associated with the presence of aluminum had free radical-mediated oxidative reaction as causative mechanism. Free radicals are in fact potent deleterious agents causing cell death or other forms of irreversible damage, e.g., free radicals appear to modify DNA base pairs causing mutagenesis, carcinogenesis and aging (Dizdaroglu et al, 2002). Neurons appear to be particularly susceptible to attack by free radicals for the following reasons: 1) their glutathione content, an important natural antioxidant, is low; 2) their membranes contain a high proportion of polyunsaturated fatty acids; and 3) brain metabolism requires substantial quantities of oxygen (Christen et al, 2000).

The mechanism of Al pro-oxidant action may be produced through its interaction with the membranes, subtle changes in the rearrangement of lipids which could attack and facilitate the propagation of lipid peroxidation leads to loss of membrane integrity, decrease its fluidity, disrupt the functioning membrane bound enzymes receptors and ion channels, which leads finally to cell death (Fraga et al, 1999). Al has increased the lipid peroxidation of platelet membrane in a dose-dependent manner via generation of reactive oxygen species (ROS) (Daniels et al, 1998). The effect of metals on free radical reaction is usually ascribed to their ability to participate in redox reactions in which they donate or accept a single electron. Aluminum, due to its electronic configuration, does not participate in redox reactions; consequently, its effect is probably due to a direct interaction with cell components, rather than to reactions with oxidative reactive species (Timbrell, 2002). Recent In vitro studies showed that incubation of Al with the human neuronal cells (NT2) produced significant apoptosis even in lower doses due to enhancing the production of cytochrome c, which trigger the cell death cascade process (Griffioen et al, 2004). Therefore one possible mechanism through which Al produces neurodegeneration is through induction of apoptosis.

In the present study, there was a significant reduction in the activities of GSH-Px, catalase, and t-SOD in brain homogenate from rats exposed to aluminum compared to control group. A reduction of SOD and catalase has been observed in cerebral hemisphere of chicks following intraperitoneal injection of Al sulphate (Swain and Chainy 1997). The mechanism of Al-mediated suppression of antioxidant enzymes was attributed to a direct interaction of aluminum with free radical scavenging enzymes. Therefore, it accentuates the oxidative insult to tissues. These enzymes represent the first line of defense against the oxygen free radical and the decrease in their activities may contribute to the oxidative stress to the brain tissues (Swain and Chainy, 1998). Therefore, one possible way of inducing neurotoxicity by Al is through a reduction in the brain activities of several antioxidant enzymes (Gupta and Shukla, 1995). The reduction of brain activity of GSH-px is in agreement with the results obtained by Atienzar et al, (1998) who demonstrated a reduction in GSH-Px activity in rat brain after inraperitoneal injection of aluminum chloride for 4 weeks. The mechanism of reduction of GSH-Px activity may be mediated via substitution of selenium by aluminum that renders the enzyme inactive (Atienzar et al, 1998).

Al plus vitamin A or riboflavin treated groups showed significant increase in the antioxidant enzymatic activities, suggesting that both vitamins may play a role in the protection against oxidative damage caused by accumulation of aluminum in brain. It has been demonstrated that supplementation of rat with beta-carotene (vitamin A precursor) minimized the harmful effect of fenvalerate and improved semen quality in rats (El-Demerdash et al, 2004a). Beta carotene, alone or in combination with vitamin E, has a protective role against lipid peroxidation in cadmium-induced toxicity in male rats (El-Demerdash et al, 2004b). Moreover, carotenoids protect against oxidative damage of lymphocytes both in vivo and in vitro by scavenging DNA-damaging free radicals and modulating DNA repair mechanism (Astley et al, 2004). The mechanism by which beta-carotene acts as antioxidant is that beta-carotene is a quencher of singlet oxygen that can directly interact with peroxyl radicals involved in lipid peroxidation (Burton and Ingold, 1985). Riboflavin deficiency in rats has been associated with significant reduction of catalase, SOD and GSH-px and consequently the increased free oxygen radicals was attributed to riboflavin deficiency (Tumkiratiwong et al, 2003).

Liver homogenate showed increased activity of GSH-Px and GR-ase; while the activities of catalase and t-SOD were decreased. This result has a partial agreement with Abubakar et al, (2003) who recorded that hepatic catalase and GR-ase levels were both reduced in animals treated with aluminum. While the GSH-Px was increased in liver homogenate, it was significantly decreased

in brain homogenate. This suggests that Al has a dual effect of oxidant and antioxidant in different tissues. It was suggested that this dual effect is depending upon iron concentration and membrane integrity (Fraga et al, 1990).

Consistent and significant reduction in the activities of serum brain function enzymes including MAO, AChE, and 5'-N were found in Al-treated group compared to control group. This result agrees with previous data recorded by Zatta et al, (1998) and Dave et al (2002). Cholinesterases are a large family of enzymatic proteins widely distributed throughout both neuronal and non-neuronal tissues. Al may interfere with various biochemical processes including acetylcholine metabolism, and can thus act as a possible etiopathogenic cofactor. Monoamine-oxidase catalyses the oxidative deamination of various primary amines, such as norepinephrine, serotonin, dopamine and others. Altogether these findings indicate that long-term Al feeding results in inhibition of AChE, and decreased activity of MAO, which could represent the mode of action through which Al may further contribute to pathological processes in Al-induced neurotoxicity.

Administration of Al plus vitamin A or riboflavin showed significant increase in the activities of brain function enzymes compared to Al-treated group, supporting their role in alleviating Al-dependent neurotoxicity.

Serum liver function enzymes including AST, ALT, GGT and ALP showed increased activities after long term administration of Al. These results are in accordance with Wilhelm et al, (1996) who found an increased release of the enzymes AST and ALT into the hepatic perfusate due to high dose of Al. this suggest that chronic Al exposure induce hepatoxicity manifested by elevation of liver function enzymes. The combination of vitamin A or riboflavin had a significant improvement in the activities in ALT and AST. Therefore, both compounds can alleviate the Al-mediated hepatoxicty in rats.

Taken together, the present findings documented that the brain is particularly susceptible to aluminum toxic effects. Al exposure significantly enhanced neuronal lipoperoxidative damage; decrease Fe, Cu, and Zn content, with concomitant alterations in the antioxidant defense status that may be responsible for a consistent rise in the cell load of oxidative stress. This may contribute, as an aggravating factor, to the development of neurodegenerative events. Combination of vitamin A or riboflavin with Al partially decreased its toxic effect and improved brain and liver function, possibly due to their antioxidant effects.

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