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Full Length Research Paper

The effects of aluminium and selenium supplementation on brain and liver antioxidant status in the rat

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This *in vivo* study was designed to investigate the potential of aluminium (Al), in the absence of added iron, to participate in either antioxidant or pro-oxidant events. Some markers of oxidative stress were determined in liver and brain of rats exposed to aluminium lactate, either alone or in the presence of dietary supplements of selenium (se) as selenite. Exposure to aluminium for 21 days resulted in a statistically significant (P<0.05) decrease in brain glutathione. However, a non-significant increase in hepatic glutathione was observed in animals supplemented with either Se or Al, but Al in combination with Se prevented this elevation. In the brain a statistically non-significant increase (P>0.05) was observed in the GSH content. Contrary to what is known, Al exposure resulted in statistically significant decrease (P<0.001) in lipid peroxidation as measured by production of malondialdehyde in both liver and brain. Aluminium exposure had no significant effect on the liver and brain superoxide dismutase activity. Results of the present study suggest that in rat aluminium exposure may have both pro-oxidant and antioxidant effect. Furthermore, Se supplementation may offer some protection against aluminium toxicity but this needs to be further elucidated.

Key words: Aluminium, selenium, rat, brain, liver, antioxidant enzymes.

INTRODUCTION

Long-term haemo-dialysis using fluids containing aluminium has been associated with encephalopathy (Alfrey et al., 1976), oesteomalacia (Parkinson et al., 1979) and anaemia (Elliott et al., 1978) due to aluminium toxicity. Dialysis dementia is characterised by speech disorders, myoclonus, coma and possibly death (McMillan et al., 1993). In experimental models of aluminium toxicity, encephalopathy, nerve cell degeneration, demyelination of the brain stem cells, and impaired motor co-ordination are observed (Ebina et al., 1984). Cerebral accumulation of aluminium has also been reported in several other neuro-pathological disorders including Alzheimer's disease (Good et al., 1992; Lukiw, 1997; Perl and Brondy, 1980), Down's syndrome (Crapper et al., 1973), amylotrophic lateral sclerosis (Gadjusek and Salazer, 1982; Perl et al., 1982)

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and the dementia of Parkinson's disease (Hirsch et al., 1991). The role of aluminium in these disorders is less clear, however high concentrations of aluminium are found in certain regions of the brains of patients with Alzheimer's disease (Kellett et al., 1986; Perl and Brody, 1980; Crapper et al., 1976; 1980). There is also an epidemiological association between aluminium in drinking water and the incidence of Alzheimer's disease (Martyn et al., 1989). Histological analysis have also revealed high concentration of aluminium in the nuclei of neurones associated with neurofibrillary tangle in Alzheimer's disease, and senile plaques (Candy et al., 1986).

Despite the ample clinical and experimental data, the mechanisms of aluminium toxicity remain largely unknown. *In vitro* and *in vivo* experimental studies have implicated the formation of reactive oxygen species in the potential neurotoxic effect of aluminium, particularly in Alzheimer's disease (Halliwell, 1992; Evans, 1993). Zaman (1994) showed that Al stimulates NADPH oxidation and takes part in the process of free radical formation. Experimental animal models and cell culture studies reveal that aluminium affects the expression of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase and glutathione (GSH) possibly leading to membrane fragility as a consequence (Julka and Gill, 1996; Oteiza et al., 1993; Campbell et al., 1999). These data support the role of oxidative stress in aluminium induced cellular dysfunction and if this is indeed the case, antioxidants, such as selenium, may be protective. The aim of the present study was to investigate the effect of administering high doses of aluminium on indices of oxidative stress in the rat and their modulation by dietary selenium.

MATERIALS AND METHODS

Experimental animal model

Twenty male Wistar albino rats weighing 170-180 g were divided into 4 experimental groups, each consisting of 5 rats:

- First group was injected (i.p.) with an aqueous solution of aluminium lactate (Johnson Matthey GmbH, Zeppelinstraβe 7, Karlsruhe, germany), at a dose of 5 mg aluminium per kg body weight per day five times per week for 3 weeks. Animals received a standard chow diet (SDS) during this time.
- The 2nd group was injected with similar volume of normal saline over the same period and received a standard chow diet *ad libitum*.
- A 3rd group of rats was injected with aluminium as for (i) but received a chow supplemented with 1 mg/kg selenium as sodium selenite (Sigma Chemical Company Poole, Dorset, UK).
- The 4th group received dietary selenium only without receiving i.p. aluminium.

All animals were individually weighed and examined daily, with food and water intakes recorded. They were all housed in polypropylene cages to avoid extraneous trace element contamination.

Animals were sacrificed by anesthetic overdose using sodium pentabarbitone (100 mg/kg). Blood was withdrawn via the dorsal vena cava into lithium heparin tubes and tissues (liver, kidney, spleen, brain and bone) removed, weighed and stored in aluminium-free plastic containers at -80^{o}C until analysis. The brain was quickly excised, rinsed with cold 0.14 M NaCl and homogenized in 25% ice cold 50 mM Tris-HCl buffer pH 7.4 (Benjamin et al., 1978).

Trace element analysis

Weighed tissue samples (0.1-0.5 g) were digested with 90% nitric acid and 70% perchloric acid for measurement of aluminium as previously described (Taylor and Walker, 1992) or nitric acid, perchloric acid and sulphuric acid in the case of selenium. Aluminium in the plasma or digested tissue samples was determined by electrothermal atomic absorption spectrometry (ETAAS) and selenium by hydride generation atomic absorption spectrometry (AAS).

Measurement of reduced glutathione

Liver and brain homogenates were diluted 10-fold with perchloric acid (70% v/v), and centrifuged for 10 min at 5,000 x g. Fifty microlitres of sample was transferred to 1.5 ml of phosphate-EDTA buffer, followed by the addition of 50 μl o-phthaldialdehyde, and after vortexing was allowed to stand at room temperature in the dark for 30 min. Thereafter the fluorescence intensity was measured using a fluoremeter with an excitation of wavelength of 340 nm, and emission wavelength of 420 nm (Hissin and Hilf, 1979).

Measurement of superoxide dismutase activity

Tissue samples (30-60 mg) were pulverized in a Braun Microdismembrator II (B Braun Biotech Inc.) in 200 μl of the homogenising buffer (50 mmol/L potassium phosphate, pH 7.4 containing 0.3 mol/L KBr and 300 μl of protease inhibitor cocktail). Homogenates were sonicated for 20 min, centrifuged for 15 min at 20,000 x g and the supernatant stored at -80^{o}C until required. The superoxide dismutase activity was determined by a direct spectrophotometric method using Randox kits as previously described by Marklund (1976, 1985).

Measurement of tissue lipid peroxidation

One hundred and fifty microliter of the tissue supernatant or 50 μl of samples were diluted to 500 μl with doubled-deionized water. 250 μl of 1.34% thiobarbituric acid was added to all the tubes followed by addition of an equal volume of 40% trichloroacetic acid. The mixture was shaken and incubated for 30 min in a boiling water bath. Tubes were allowed to cool to room temperature and the absorbances read at 532 nm using zero concentration as blank (Gutteridge and Quilan, 1983; Hartman, 1983).

Protein determination

The total protein content of tissue homogenate was determined according to the method of Lowry et al. (1951).

Table 1. Aluminium and Selenium Concentration injected with these metals.

Group	Aluminium			Selenium		
	Plasma (µg/L)	Liver (µg/g)	Brain (µg/g)	Plasma (µg/L)	Liver (µg/g)	Brain (µg/g)
Control	3.28 ± 0.3	0.159 ± 0.0	0.02 ± 0.0	562 ± 49.1	7.00 ± 0.4	1.35 ± 0.0
Al	218 ± 47.5$^{***, ***}$	29.48 ± 3.4$^{**, *}$	1.83 ± 0.3$^{a+ b*}$	384 ± 51.3$^{*, *}$	6.50 ± 0.2	1.47 ± 0.0
Se	3.00 ± 0.1	0.177 ± 0.0	0.15 ± 0.0	515 ± 26.7	8.40 ± 0.9	1.35 ± 0.1
Al + Se	203 ± 36.1$^{**, **}$	11.83 ± 2.54*	0.61 ± 0.2#	603 ± 52.8 #	9.00 ± 0.3#	1.49 ± 0.1

Values are means ± SEM for (n=5). Comparison was assessed for signifficance using one way ANOVA and unpaired t-tests for normal distributed data.
* P<0.05, ** P<0.001, and *** P<0.001 compared to control.
* P<0.05, ** P<0.001, and *** P<0.001 compared to selenium treated group.
# P<0.05, ## P<0.001, and ### P<0.001 compared to aluminium treated group.

Table 2. Tissue Protein and Malondialdehyde content injected with Al and Se.

Group	Protein (mg/g tissue)		Malondialdehyde content (nmoles MDA/mg protein)	
	Liver	Brain	Liver	Brain
Control	169.7 ± 5.6	42.8 ± 0.5	0.2 ± 0.019	3.7 ± 0.2
Al	150.9 ± 5.3*	51.9 ± 0.9***	0.1 ± 0.019**	2.2 ± 0.1***
Se	167.3 ± 7.8	50.0 ± 0.8**	0.1 ± 0.012**	2.3 ± 0.2***
Al + Se	160.6 ± 10.4	49.5 ± 1.3***	0.1 ± 0.024*	2.0 ± 0.1***

Values are means ± SEM for (n=5). Comparison was assessed for signifficance using one way ANOVA and unpaired t-tests for normal distributed data.
* P<0.05, ** P<0.001, and *** P<0.001 compared to control.
* P<0.05, ** P<0.001, and *** P<0.001 compared to selenium treated group.
# P<0.05, ## P<0.001, and ### P<0.001 compared to aluminium treated group.

Statistical analysis

Data were expressed as mean ± standard error of the mean (SEM) and results tested for statistical significance using unpaired Student's t-test's or one way analysis of variance (ANOVA).

RESULTS

Plasma aluminium concentrations were significantly higher ($P < 0.01$) in both of the groups treated with aluminium (Table 1). Plasma selenium concentrations were significantly lower in the rats receiving aluminium alone compared to other groups.

The aluminium content of brain and liver was also significantly increased in both aluminium-treated groups ($P < 0.01$). Treatment with dietary selenium was associated with a significant reduction ($P < 0.05$) in brain and liver aluminium content (Table 1).

Plasma selenium concentrations were not significantly different in rats receiving dietary selenium supplements alone ($P > 0.05$). Aluminium treatment was associated with a lower selenium concentration compared to controls ($P < 0.05$) in plasma and liver. Liver selenium concentration was significantly higher in animals receiving selenium and aluminium compared to those receiving aluminium alone ($P < 0.05$) (Table 1).

The protein content of liver tissue was decreased in the aluminium-treated group but no significant differences were seen between the other groups. In the brain however, there was a significant increase in all of the treated groups in comparison to the control ($P < 0.01$) (Table 2).

The malondialdehyde content (a measure of lipid peroxidation) was significantly lower in liver ($P < 0.05$) (Table 3) and brain ($P < 0.01$) of rats receiving aluminium and/or selenium. The GSH content in the brain revealed

Table 3. Superoxide dismutase activity and Reduced glutathione injected with Al and Se.

Group	*Superoxide dismutase activity* (units/mg protein)		Reduced glutathione (nmoles GSH/mg protein)	
	Liver	Brain	Liver	Brain
Control	9.2 ± 0.6	2.6 ± 0.1	1.1 ± 0.1	3.8 ± 0.3
Al	9.6 ± 0.9	2.3 ± 0.2	1.3 ± 0.1	4.0 ± 0.2
Se	7.4 ± 0.7	2.1 ± 0.1	1.3 ± 0.1	4.8 ± 0.2
Al + Se	10.1 ± 1.2	2.3 ± 0.1	1.2 ± 0.1	4.3 ± 0.2

Values are means ± SEM for (n=5). Comparison was assessed for signifficance using one way ANOVA and unpaired t-tests for normal distributed data.
* P<0.05, ** P<0.001, and *** P<0.001 compared to control.
* P<0.05, ** P<0.001, and *** P<0.001 compared to selenium treated group.
# P<0.05, ## P<0.001, and ### P<0.001 compared to aluminium treated group.

a statistically non-significant increase in all of the groups. Hepatic and brain SOD were not significantly affected by treatment with aluminium or selenium (Table 3).

DISCUSSION

A search for the understanding of the cellular and molecular basis of aluminium toxicity has stimulated very many experimental studies. A possible role of oxygen radicals in neurodegenerative diseases has been a topic of burgeoning research investigation. In the present *in vivo* studies an attempt has been made to delineate the potential of aluminium to participate independently without iron as an antioxidant and pro-oxidant.

Intraperitoneal administration of aluminium resulted in a significant increase in plasma and tissue aluminium concentration. There was no signs or symptom of toxicity in the animals, apart from reduction in food and water intake. This supports the observation of Van der Voet et al. (1992) who reported accumulation of aluminium in rat liver after intraperitoneal injection of $AlCl_3$. However, the relationship between tissue aluminium levels and Al toxicity is highly complicated because elevated tissue aluminium levels does not necessarily produced detrimental effects. However, during autopsy of the rats in this study, the only gross pathological changes observed were in the aluminium treated groups. There were smooth, solid and white inclusions, which were about 3 mm x 2 mm in size, either floating freely in the abdominal cavity or attached to an abdominal organ such as liver and spleen. Aluminium is, neverthyeless, toxic to man and other vertebrates (Alfrey et al., 1980).

Generally, selenium treatment alone showed no significant difference from the control. This may be due to high level of selenium found in normal rat diet (0.5 mg/kg). This amount might be incorporated into SH-proteins. Over 80% of aluminium in serum/plasma is bound to transferrin, a major serum binding protein. Some of the observed effects of aluminium were completely abolished by Se-supplementation. These suggest that Se have an effect on aluminium distribution within the tissues. Since the effects were not observed in the plasma, Se supplementation may not have any effect on aluminium excretion.

We observed no significant changes in SOD activity after Al-exposure. But Rudenko (1999) reported that the Se group showed a different response. However, the lack of significant changes in SOD activity after aluminium exposure is supported by the work of Chainy et al, (1996). This indicates that the dietary Se supplementation has less influence on the brain. It is really difficult to determine precisely the exact aluminium-Selenium interaction in this case. However, one can suggest that in the presence of aluminium, Selenium is being depleted from the tissues due to aluminium burden. Since Selenium can cause an increase in protein via increasing the levels of selenoprotein, particularly the thiol containing proteins, notably the glutathione and its enzyme related forms, which are most sensitive to alterations in selenium status.

The potential role of aluminium involvement in oxidation activities remains controversial to-date. Evidence for (Oteiza et al., 1993; Exley, 1999; Evans, 1993) and against (Xie et al., 1995; Oteiza et al., 1993) its potential involvement has both been reported. The present work contributes to the existing debate on aluminium as antioxidant at low concentration and pro-oxidant at high concentration. Similarly, suggesting that aluminium might facilitate membrane peroxidation by increasing their susceptibility to free radical induced damage (Van Rensburg et al., 1997; Ohyashiki et al., 1998).

The data are difficult to interpret, as the result in the liver is completely the reversed of what was observed in the brain. Nevertheless, the liver result is in conformity to the report of Bondy et al. (1998). The decrease in MDA

production in both liver and brain are contrary to most published reports (Yoshino et al., 1999; Chainy et al., 1996; Meglio and Oteiza, 1999). Although under certain conditions free aluminium ion has been reported to inhibit malondialdehyde production (Oteiza et al., 1993). Most workers incorporate iron in their studies to cause aluminium to exert its deleterious pro-oxidant effects. There is no doubt that aluminum has the potential to cause both oxidative and antioxidative effects which explain why some workers reported a more profound effect of aluminium oxidative effects in the presence of iron rather than aluminium alone. Hence if aluminium induces reactive oxygen species this would eventually lead to a cascade chain of reaction leading to toxicity. Therefore, an antioxidant could reduce aluminium-induced toxicity.

The dual or biphasic effect of aluminium exposure observed in these experiments is probably due to direct interaction of aluminium with cellular components, rather than to reaction with oxidative-reactive species. Biphasic effect of aluminium has been reported in diverse cell system including phosphorylation of neurofilament sub-units (Letterier et al., 1992). The effect may be due to the formation of aluminium complexes with indirect effect on free radical scavenging enzymes and glutathione.

From the presented *in vivo* studies, it can be concluded that aluminium exposure may have some potential to promote pro-oxidant event and that Se-supplementation may likely help in preventing these deleterious pro-oxidant effect. However, these need to be further substantiated.

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