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A Systematic Review on Oxidant/Antioxidant Imbalance in Aluminium Toxicity

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Abstract: The purpose of this study was to provide a systematic review on the animal or human evidences linking aluminium (Al) toxicity to oxidant/antioxidant imbalance. Embase, Scopus, Pubmed, Web of Science, Google Scholar and SID databases were searched up to 1st October 2010. Over 50 studies including animal and human linking oxidative stress to Al were reviewed. Most of animal and human studies show a significant increase in lipid peroxidation (LPO) by Al. The maximum LPO was reported in the brain. Data about changes of enzymatic antioxidants such as Superoxide Dismutase (SOD), Catalase (CAT), Glutathione Peroxidase (GPx) post exposure to Al are controversial. Animal studies showed that vitamin E, C, melatonin and pinoline reduce LPO in Al-exposed subjects. Al can affect body oxidant/antioxidant balance in favor of oxidative toxic stress. Among parameters tested in various studies, LPO seems the best indicator of Al toxicity. The role of iron homeostasis in mediation of cytotoxic effects of Al seems important. Since, oxidant/antioxidant imbalance is involved in the pathogenesis of many diseases including inflammatory bowel diseases, diabetes, osteoporosis, it would not be surprising to track roles of Al in many deliberating diseases in future.

Key words: Metals, aluminium, oxidant/antioxidant balance, oxidative stress, reactive oxygen species

INTRODUCTION

Oxidative Stress (OS) can be defined most simply as the imbalance between the production of Reactive Oxygen Species (ROS) capable of causing peroxidation of lipid layer of cells and the body's antioxidant defense (Halliwell and Gutteridge, 1997). Excessive generation of ROS leads to damage of cellular lipid membrane, proteins and DNA. Several mechanisms exist in the body to cope overproduction of free radicals. The basic and the most prominent defense mechanism of the human body is antioxidants that are involved in prevention, repairing and physical defense against oxidants. Antioxidants are generally categorized to non-enzymatic and enzymatic. Non-enzymatic antioxidants include dietary compounds (vitamins C and E), minerals (selenium and zinc), glutathione, uric acid and ubiquinol. Superoxide Dismutase (SOD), Catalase (CAT) and Glutathione Peroxidase (GPx) are the main enzymatic antioxidants (Abdollahi *et al*., 2004; Rezaie *et al*., 2007).

Metals as a part of the earth crust are redistributed naturally in the environment by both geologic and biologic cycles. Although, elements can be toxic at high doses but some of them are essential components of biological structures. Recent studies have shown that metals can produce ROS resulting in Lipid Peroxidation (LPO), DNA damage, depletion of sulfhydryls and altered calcium homeostasis. Generally toxicity of metals specially the transition metals is mediated through generation of ROS, LPO, DNA cleavage and decrease in antioxidant potential (Malekirad *et al*., 2010).

Aluminium (Al) is the most abundant metal and the third most common element in the earth crust. Although, Al is a common constituent of the environment, it has no recognized biological function in the body. Unfortunately, the sources of Al are largely unknown to the public. In addition to occurring naturally in food and water, Al is added to drinking water, many processed foods, cosmetics, toothpaste, antiperspirants and adjuvants in various parenteral preparations and pharmaceutical agents (Becaria *et al*., 2002; Pournourmohammadi *et al*., 2008).

Al is considered a pro-oxidant and in exposure results in the production of free radicals (Halliwell and Gutteridge, 1990; Ranjbar *et al*., 2008), being responsible for neurotoxicity. Al induces OS by changes in the levels of SOD, CAT and biomarkers of cellular peroxidation (Yousef, 2004). There has been considerable debate in role of chronic exposure to Al in neurodegenerative disorders such as Alzheimer (Zatta, 2006; Gupta *et al*., 2005), Parkinson disease and dementia (Erasmus *et al*., 1995) and hepatotoxicity (Chinoy and Parker, 1999). The toxic effects of Al appear to be mediated, at least in part, by free-radical generation (Moumen *et al*., 2001; Anane and Creppy, 2001).

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In this systematic review, all evidences from animal and human studies relating toxicity of Al and OS were evaluated.

MATERIALS AND METHODS

Data sources: Embase, Scopus, Pubmed, Web of Sciences, Google Scholar and SID were searched up to 1 October of 2010 for studies investigating Al-induced oxidant/antioxidant imbalance in humans or animals. The search terms were oxidant or antioxidant or oxidative stress and aluminium. The reference lists of articles were also reviewed for additional relevant studies.

Study selection

Inclusion criteria: All of the Al-induced OS studies in human and animal with key outcomes of change in oxidant/antioxidant imbalance parameters were included.

Exclusion criteria: Reviews or letters and unpublished data such as thesis were excluded.

RESULTS

Human studies: Of publications in the initial database search, 10 trial studies on the efficacy of Al on OS were reviewed. Information of these clinical trials is summarized in the Table 1. The human studies showed that Al has lately been implicated as one of the possible causal factors contributing to neurodegenerative disorders according to OS potential of Al in the brain (Bulat *et al*., 2008; Valentini *et al*., 2007; Liao *et al*., 2006; Sargazi *et al*., 2006; Bonnefont-Rousselot *et al*., 2004; Anane and Creppy, 2001; Abou-Seif, 1998; Ongajooth *et al*., 1996). The relation between Al toxicity and OS were studied in blood samples obtained from Al-exposed workers (Ranjbar *et al*., 2008; Menevse *et al*., 2006; Ferretti *et al*., 2003).

Also LPO was increased by exposure to Al in all of studies but data on SOD, CAT and GPx activity in exposure to Al are controversial. In half of studies, SOD, CAT and GPx activities were increased and in other half were reduced.

Animal studies: The details of the animal studies that investigated OS effects of Al are summarized in Table 2. Twenty-five trials on the efficacy of Al on OS were reviewed. The research results showed a significant increase in LPO and inhibition of antioxidant enzymes by Al in plasma, liver, brain, testes, kidney, renal cortex, biliary, serum, erythrocyte, hepatocyte, intestine and sperm of Al-treated rabbits, rats and mice (Stevanovic *et al*., 2009; Bhalla and Dhawan, 2009; Prakash and Kumar, 2009; Sanchez-Iglesias *et al*., 2009; Mahieu *et al*., 2009; Ranjbar *et al*., 2008; Luo *et al*., 2007; Gonzalez *et al*., 2007; Sharma *et al*., 2007; Kutlubay *et al*., 2007; Albendea *et al*., 2007; Abd-Elghaffar *et al*., 2005; Nehru and Anand, 2005; Orihuela *et al*., 2005; Abubakar *et al*., 2004; El-Demerdash, 2004; Mahieu *et al*., 2003; Zatta *et al*., 2002; Moumen *et al*., 2001; Anane and

Table 1: Human studies considering the presence of oxidative stress in aluminium exposure

Study	Specimen	Result	Disease
Ranjbar *et al*. (2008)	Blood	LPO↑	
		TAP↓	
		SH↓	Workers exposure to Al (45 workers)
Bulat *et al*. (2008)	Erythrocytes	LPO↑	
		G6PDH↓	
		GR↓	
		GPX↑	
		CAT↑	
		SOD↓	Workers exposure Al (59 Workers and 75 control)
Valentini *et al*. (2007)	Blood	LPO↑	Haemodialysis (37 HD pateints and 20 control)
Menevse *et al*. (2006)	Blood	SOD↑	
		LPO↑	Haemodialysis (47 HD pateints and 23 control)
Liao *et al*. (2006)	Plasma	LPO↑	Workers exposure to Al (103 workers and 67 control)
Sargazi *et al*. (2006)	Brain,	LPO↑	
	Bone	GSH↓	
		GPX↓	*In vitro* (HDL isolated from human plasma)
Bonnefont-Rousselot *et al*. (2004)	Plasma	GPX↓	Macrophagic Myofasciitis (30 MMF patients and 38 control)
Abou-Seif (1998)	Erythrocyte and RBC	LPO↑	
		CAT↑	
		NADH and NADPH oxidation↑	
		SOD↑	Healthy human
Ongajooth *et al*. (1996)	Kidney	GPX↓	
		CAT↓	Chronic Renal Disease (54 patients and 32 control)

SOD: Superoxide dismutase, LPO: Lipid peroxidation, GSH: Glutathione, GPX: Glutathione peroxidase, CAT: Catalase, GR: Glutathione reductase, G6PDH: Glucose-6-phosphate dehydrogenase, TAP: Total antioxidant power, SH: Total thiol molecules

Table 2: Animal studies considering the presence of oxidative stress that induced by aluminium

Study	Model	Specimen	Result
Bhalla and Dhawan (2009)	Rat	Brain	LPO↑
			ROS↑
			CAT↑
			SOD↑
			GR↑
			GSH↑
Mahieu *et al.* (2009)	Rat	Kidney	LPO↑
			GSH↓
			GPX↓
			CAT↓
Sanchez-Iglesias *et al.* (2009)	Rat	Brain	LPO↑
			SH↑
			SOD↓
			GPX↓
			CAT↓
Prakash and Kumar (2009)	Rat	Brain	LPO↑
			GSH↑
			SOD↓
			CAT↓
Stevanovic *et al.* (2009)	Rat	Brain	LPO↑
			ROS↑
			GSH↓
Luo *et al.* (2007)	Rat	Brain	SOD↓
			LPO↑
Yousef *et al.* (2007)	Rabbit	Sperm	FR↑
			LPO↑
			SOD↓
			CAT↓
Gonzalez *et al.* (2007)	Rat	Biliary	LPO↑
			GSH↓
			GPX↓
			CAT↓
Sharma *et al.* (2007)	Rat	Serum, Brain	GST↑
			GR↓
			GPX↓
			CAT↓
			SOD↓
			AChE↓
			LPO↑
			GSH↓
Abd-Elghaffar *et al.* (2005)	Rabbit	Brain	LPO↑
			SOD↓
Nehru and Anand (2005)	Rat	Brain	LPO↑
			CAT↑
			SOD↑
Orihuela *et al.* (2005)	Rat	Intestine	GSH↓
			LPO↑
			GST↓
El-Demerdash (2004)	Rat	Brain, Plasma, Testes, Kidney, Liver	LPO↑
			AChe↓
Yousef (2004)	Rabbit	Plasma, Liver, Brain, Testes, Kidney	FR↑
			GST↓
			SH↓
			AChE↓
Abubakar *et al.* (2004)	Rat	Brain	CAT↓
			GSH↓
			ROS↑
Mahieu *et al.* (2003)	Rat	Renal cortex	GSH↓
			GST↓
			LPO↑
Zatta *et al.* (2002)	Mouse	Brain	AChE↑
Moumen *et al.* (2001)	Rat	Plasma, Liver, RBC	GPX↓
			SOD↑
Amador *et al.* (2001)	Rat	Brain	LPO↑
Yoshino *et al.* (1999)	Rat	Liver	LPO↑
Katyal *et al.* (1997)	Rat	Brain	SH↓
			GR↓

Table 2: Continued

			ATPase↓
			GST↓
Verstraeten *et al.* (1997)	Rat	Brain	LPO↑
Xie and Yokel (1996)	Bovin	Brain	LPO↑
Julka and Gill (1996)	Rat	Brain	LPO↑
			SOD↓
			CAT↓
			GPX↓
Chainy *et al.* (1996)	Rat	Liver	LPO↑
			CAT↓
Oteiza *et al.* (1993)	Mouse	Brain	LPO↑
Fraga *et al.* (1990)	Mouce	Brain, Liver	LPO↑

AChE: Acetylcholinesterase, SOD: Superoxide dismutase, LPO: Lipid peroxidation, GSH: Glutathione, GPX: SH: Total thiol molecules, glutathione peroxidase, CAT: Catalase, GR: Glutathione reductase, G6PDH: Glucose-6-phosphate dehydrogenase, GST: Glutathione-S-teransferase, TAP: Total antioxidant power, SH: Total thiol molecules, FR: Free radical, ROS: Reactive oxygen species

Table 3: Antioxidants with protective effect on Al-induced oxidative stress

Study	Model	Specimen	Antioxidant
Yousef *et al.* (2007)	Rabbit	Sperm	Vitamin E
Kutlubay *et al.* (2007)	Rat	Liver	Vitamin E
Albendea *et al.* (2007)	Rat	Synaptosomal membrane	Melatonin
Nehru *et al.* (2007)	Rat	Brain	Centrophenoxine
Jyoti and Sharma (2006)	Rat	Brain	Bacopa monniera
Sharma and Mishra (2006)	Rat	Brain	Tiron and glutathione
Kowalczyk *et al.* (2005)	Men with hipercholesterolaemia	RBC	Anthocyanins
Yousef (2004)	Rabbit	Plasma, liver, brain, testes, kidney	Vitamin C
Millan-Plano *et al.* (2003)	Rat	Synaptosomal membrane	Melatonin and pinoline
Swain and Chainy (2000)	Chick	Brain	Tiron, EDTA

Creppy, 2001; Amador *et al*., 2001; Yoshino *et al*., 1999; Katyal *et al*., 1997; Verstraeten *et al*., 1997; Chainy *et al*., 1996; Xie and Yokel, 1996; Julka and Gill, 1996; Oteiza *et al*., 1993; Fraga *et al*., 1990). Data on the effect of Al on SOD are controversial. Studies indicated that CAT and GPx activities in AL-treated animals are reduced. In brain, maximum LPO was observed but it was not associated with alterations in antioxidant enzymes activity.

Drugs used as antioxidants with protective effect on Al-induced OS are shown in Table 3. In consideration of the strong evidence of OS in Al exposure, antioxidant therapy deserves a place in protection against Al toxicity (Kutlubay *et al*., 2007; Albendea *et al*., 2007; Nehru *et al*., 2007; Jyoti and Sharma, 2006; Sharma and Mishra, 2006; Kowalczyk *et al*., 2005; Millan-Plano *et al*., 2003; Swain and Chainy, 2000).

DISCUSSION

OS occurs when there is an excessive free radical production and/or low antioxidant defense and results in chemical alterations of bio-molecules, which cause structural and functional modifications (Massyand Khoa, 2002). In response to OS, a great diversity of aldehydes are formed in biological system that oxidize polyunsaturated fatty acids leading to LPO. Furthermore, these aldehyde metabolites lower the body defense system especially by disturbance of SOD (Esterbauer *et al*., 1991).

The brain is particularly vulnerable to oxidative damage, due to its high oxygen consumption and high contents of easily oxidisable lipids and transition metal ions, capable of catalyzing the formation of ROS (Bush, 2000). Brain tissue from patients with Alzheimers disease contains high levels of LPO (Lovell *et al*., 1997; Sayre *et al*., 1997) and protein oxidation products (Smith *et al*., 1991). An association between LPO in the brain and CNS and occurrence of some disease like Alzheimers has been reported (Xie and Yokel, 1996).

Al seems to be transferred directly or after disruption of the Blood Brain Barrier (BBB) to the brain. It seems that physiological ligands that present at these barriers are altered in several disease states, thus result in an increased Al exposure (Yokel, 2000). The pro-oxidant effects of Al can damage the neuronal membrane by altering the physical properties of membrane, interfering with the functioning of voltage-activated ionic channels or altering the secretion of transmitters (Lebel and Bondy, 1991; Donald *et al*., 1989). Al is not a transition metal and therefore cannot initiate peroxidation but after binding to transferrin reduces the binding of iron to its protein resulting in an increased concentration of free iron in the intracellular stores. Studies have shown that this free intracellular iron can cause the peroxidation of membrane lipids resulting in membrane damage (Mousavi *et al*., 2010; Esterbauer *et al*., 1991). However, this premise has been challenged because Al may enhance Fe^{2+}-dependent membrane LPO (Bondy and Kirstein, 1996; Gutteridge *et al*., 1985). Also, *in vitro* studies have

indicated that Al greatly accelerates iron-mediated LPO under acidic and neutral conditions (Xie and Yokel, 1996; Oteiza *et al*., 1993). LPO of biological membranes results in the loss of membrane fluidity, changes in membrane potential, increase in membrane permeability and alterations in receptor functions. A significant increase in whole brain thiobarbituric acid reactive substances after stimulation by Al salts has been reported (Julka and Gill, 1996). Moreover, the amount of Al found in ferritin extracted from Alzheimer's disease brain samples was 5.6 times higher than that of ferritin from matched control samples (Fleming and Josh, 1987). The increase may have been due to a general increase in the availability of Al to the brain of patients with Alzheimer's disease and raised the possibility that Al releases iron and Fe^{3+}.

The increased LPO is, at least in part, due to an inhibition of SOD in the brain. The result is a substantial increase in the rate of phospholipid peroxidation in brain cells, leading to membrane damage and neuronal death. SOD presents the first line of defense against superoxide, as it dismutases the superoxide anion to H_2O_2 and O_2. Because the SOD enzyme generates H_2O_2, it works in collaboration with H_2O_2 removing enzymes. CAT converts H_2O_2 to water and oxygen. CAT is present in the peroxisomes of mammalian cells and probably serves to destroy H_2O_2 generated by oxidase enzymes located within these subcellular organelles (Campbell *et al*., 1999; Luck, 1971).

Several experiments have shown that Al can affect glutathione (GSH) levels, both *in vivo* and *in vitro* (El-Demerdash, 2004; Anderson, 1998). Inside the cell, more than 98% of GSH is found in the reduced form, supported by the activity of Glutathione-Reductase (GR) which converts oxidized glutathione (GSSG) generated during OS, into the reduced GSH (Wang and Ballatori, 1998; Anderson *et al*., 1985). Glutathione-S-transferase (GST) performs an important role in the detoxification of reactive metabolites catalyzing their conjugation with GSH (Aw *et al*., 1991). Al might affect the synthesis of GSH by decreasing the activity of GS, leading to a reduced GSH content. Likewise, a slowing down in the GSH oxidized-to-reduced form by Al could explain the increment in GSSG/GSH ratio. On the other hand, it has been demonstrated that Al is able to inhibit NADPH-generating enzymes such as glucose 6-phosphate dehydrogenase and NADP-isocitrate dehydrogenase (Zatta *et al*., 2000). Since the reduced NADP is a main factor for the GSH regeneration, the decreased GSH level could be ascribed to insufficient supply of NADPH.

Al has been shown to have a strong affinity for inorganic phosphate, citrate, acetate, lactate, chloride, ATP, salicylates and many other ligands, but its direct binding to thiol group is relatively weak (Martin, 1992). Al is also shown to inhibit Mg^{2+}-ATPase activity. The decrease in ATPase activity can result in inhibition of NADPH synthesis from the glucose-6-phosphodehydrogenase system (Zaman *et al*., 1990). This could result in the storage of GR substrate, i.e., NADPH, which in turn might lower the reduction of oxidized GSH.

Cholinesterases are a large family of enzymatic proteins widely distributed throughout both neuronal and non-neuronal tissues. In Alzheimer's disease, analytical as well as epidemiological studies suggest an implication of an abnormal focal accumulation of Al in the brain. In Alzheimer's disease, Al may interfere with various biochemical processes including acetylcholine metabolism and can thus act as a possible etiopathogenic cofactor. Acetylcholinesterase exists in several molecular forms that differ in solubility and mode of membrane attachment rather than in catalytic activity (Gholivand *et al*., 2008, 2009). Kinetics measurement of acetylcholinesterase activity in the absence and presence of Al has been reported, thus it can be related to possible implication of Al in some neurodegeneration diseases.

There is evidence that Al may cause nuclear dissolution, chromosomal stickiness and interference with DNA replication (Ezaki *et al*., 2000; Martin, 1992). Studies on the gene expression induced by Al treatments demonstrated that Al stress activates at least 30 general stress genes (Hamilton *et al*., 2001). Some of these genes encode antioxidant enzymes (e.g., glutathione-S-transferase, ascorbate peroxidase, CAT and SOD) suggesting common mechanism induced by Al treatment and OS (Rodriguez Milla *et al*., 2003; Hamilton *et al*., 2001). However, this mechanism is not yet known and little evidence for the formation of ROS during Al treatment has yet been documented (Sivaguru *et al*., 2003).

Drugs used as antioxidants with protective effect on Al-induced OS are shown in Table 3. For example it has been reported a partial protection by vitamin E against Al-induced hepatotoxicity in the rat and rabbit (Yousef *et al*., 2007; El-Demerdash, 2004). These effects of vitamin E may be linked to its chain breaking antioxidant properties. Also, vitamin E, a major lipid-soluble antioxidant belonging to tocopherol, is the most effective chain breaking antioxidant within cell membrane. It is able to repair oxidizing radicals directly, preventing the chain prop against step during LPO (Yousef *et al*., 2007).

As a matter of fact, since OS is involved in the pathogenesis of many diseases including inflammatory bowel diseases (Hosseini-Tabatabaei and Abdollahi, 2008; Ghafari *et al*., 2006; Jahanshahi *et al*., 2004),

diabetes (Mohseni-Salehi-Monfared *et al*., 2009a,b; Rahimi *et al*., 2005, 2010; Radfar *et al*., 2005; Afshari *et al*., 2004), osteoporosis (Yousefzadeh *et al*., 2006) and other oxidant-related diseases (Hasani-Ranjbar *et al*., 2009, 2010; Vakilian *et al*., 2009; Ranjbar *et al*., 2007; Rahimi and Abdollahi, 2007; Malekirad *et al*., 2005), so it would not be surprising to track roles of Al in other deliberating diseases in future.

In conclusion the exact mechanism of Al toxicity is not yet known but accumulating evidences suggest this metal can potentiate oxidative and inflammatory events by activating ROS generation that eventually leads to tissue damage. Also, the effects of Al in manifestation of neurodisorders may arise from its interaction with the nervous system in various ways, which one of them is induction of oxidative damage through LPO of brain phospholipids.

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