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Review

Oxidative stress and mitochondrial dysfunction in aluminium neurotoxicity and its amelioration: A review

Vijay Kumar [a], Kiran Dip Gill [a,b,*]

[a] Department of Biochemistry, Maharshi Dayanand University, Rohtak, India
[b] Department of Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh, India

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ABSTRACT

Aluminium is light weight and toxic metal present ubiquitously on earth which has gained considerable attention due to its neurotoxic effects. The widespread use of products made from or containing aluminium is ensuring its presence in our body. There is prolonged retention of a fraction of aluminium that enters the brain, suggesting its potential for accumulation with repeated exposures. There is no known biological role for aluminium within the body but adverse physiological effects of this metal have been observed in mammals. The generation of oxidative stress may be attributed to its toxic consequences in animals and humans. The oxidative stress has been implicated in pathogenesis of various neurodegenerative conditions including Alzheimer's disease and Parkinson's disease. Though it remains unclear whether oxidative stress is a major cause or merely a consequence of cellular dysfunction associated with neurodegenerative diseases, an accumulating body of evidence implicates that impaired mitochondrial energy production and increased mitochondrial oxidative damage is associated with the pathogenesis of neurodegenerative disorders. Being involved in the production of reactive oxygen species, aluminium may impair mitochondrial bioenergetics and may lead to the generation of oxidative stress. In this review, we have discussed the oxidative stress and mitochondrial dysfunctions occurring in Al neurotoxicity. In addition, the ameliorative measures undertaken in aluminium induced oxidative stress and mitochondrial dysfunctions have also been highlighted.

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* Corresponding author at: Department of Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India. Tel.: +91 0172 2755177; fax: +91 0172 2744401/2745078.
E-mail address: kdgill2002@yahoo.co.in (K.D. Gill).

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1. Introduction

Aluminium (Al) is among the most abundant elements on earth which has gained easy access to humans. Al exists in only one oxidation state (+3), and does not undergo oxidation reduction reactions. It can react with other metals in the environment to form various complexes. Exposure to this light weight and toxic metal is ensured mainly *via* air, food and water (Ochmanski and Barabasz, 2000). Al sulfate used for purifying water is also an important source of Al burden in the body. The increasing use of Al containing products is ensuring its presence in our body. Absorption of Al is influenced by pH, organic acids, such as citrate and lactate. It has been reported that only 10% of the ingested Al is absorbed (Gorsky et al., 1979). Al has been shown to accumulate in various mammalian tissues such as brain, bone, liver and kidney (Wills et al., 1993; Sahin et al., 1994). Al does not appear to have any role in animal and human biology but its increased biological availability has been linked to both acute and chronic diseases in humans (Yokel, 2000; Exley, 2001, 2005).

An accumulating body of evidence in the progressive years has confirmed the fact that Al can have severe toxic effects (Fig. 1). Al incorporates into the bone and causes physiochemical mineral dissolution as well as cell mediated bone resorption (Bushinsky et al., 1995). Uraemic patients on chronic dialysis together with a phosphate binding buffer regimen can suffer from severe Al intoxication and develop microcytic anaemia without iron deficiency (Short et al., 1980; Touam et al., 1983). Various studies have indicated neuropathological, neurobehavioral, neurophysical and neurochemical changes following Al exposure (Miu et al., 2003; Colomina et al., 2002; Kaur et al., 2006; Walton, 2012, 2013). Al has also been shown to accumulate in the medial striatum, corpus callosum and cingulate bundleand causing learning impairment (Platt et al., 2001). The brain is considered to be most vulnerable to the toxic manifestations of Al owing to the non-dividing nature of the neurons. Further, brain is particularly sensitive to oxidative stress due to increased level of free radicals and decreased level of antioxidants following toxic insult. Al is considered to have a strong prooxidant activity inspite of its non-redox status (Exley, 2004; Zatta et al., 2002a,b). It causes oxidative damage by binding to pro-oxidant metals like iron, copper and modulates their ability to promote metal-based oxidative events. Also, Al can directly compete with and even substitute for several other essential metals *in vivo* (Zatta et al., 2002a,b). Strong evidence is there that Al forms Al-superoxide anion complex, which is a more potent oxidant than superoxide anion on its own and promotes the formation of hydrogen peroxide and hydroxyl radicals further contributing to an oxidizing environment by generating oxidative stress (Exley, 2004; Mahdi et al., 2006).

A growing evidence sustains the hypothesis that mitochondrial dysfunction may play an important role in the pathogenesis of many neurodegenerative disorders (Leuner et al., 2007). Mitochondria support the energy-dependent regulation of various cell functions, including intermediary metabolism, protein folding, cell motility and cell proliferation (Wallace et al., 1999). The primary function of mitochondria is oxidative metabolism and any defects in ATP generating capacity lead to energy failure, cellular dysfunction and eventually cell death as seen in various neurodegenerative diseases (Beal, 1996). Mitochondrial degeneration is one of the earliest signs of Alzheimer's disease (AD); appearing before the neurofibrillary tangles are evident (Hirai et al., 2001) and any oxidative damage to the mitochondria may be relevant to the pathogenesis of AD (Readnower et al., 2011). Evidence from postmortem AD brains also shows alterations in the expression of mitochondrial fission and fusion proteins (Castellani et al., 2002). Increased free radical induced oxidative stress has been associated with the development of such disorders. It has been proposed that the toxic effects of Al are mediated by free-radical generation (Bush, 2000; Campbell et al., 1999; Kumar et al., 2008) and toxic consequences resulting in mitochondrial dysfunction may ensure oxidative damage leading to oxidation of mitochondrial DNA, proteins and lipids.

2. Neurotoxicity of aluminium

The almost ubiquitous presence of Al in the environment and its increasing use in the food processing, medicines and pharmaceutical industry have presented considerable interest in the mechanisms of its varied neurotoxic effects. Because of its chemical activity, Al is not found naturally in its free or metallic state. However, in its ionic or combined forms it is ubiquitous

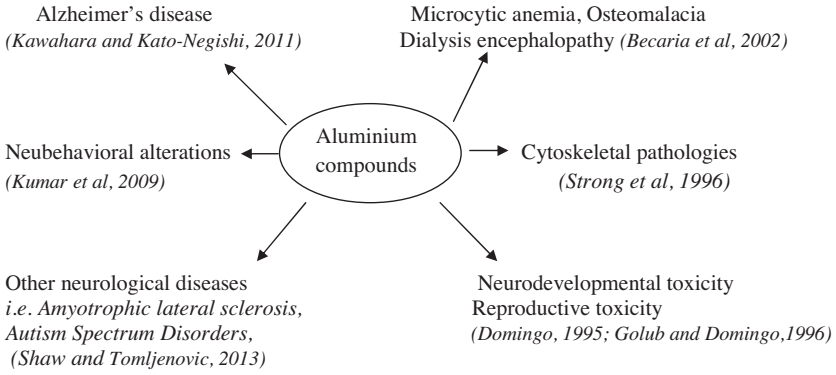

Fig. 1. Summary of toxicity of aluminium compounds in rodents and humans. The citation in parentheses denotes review articles that have compiled the pathophysiology of aluminium. (Domingo (1995); Golub and Domingo (1996); Shaw and Tomljenovic (2013)).