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Review

Multifaceted effects of aluminium in neurodegenerative diseases: A review

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ABSTRACT

Aluminium (Al) is the most common metal and widely distributed in our environment. Al was first isolated as an element in 1827, and its use began only after 1886. Al is widely used for industrial applications and consumer products. Apart from these it is also used in cooking utensils and in pharmacological agents, including antacids and antiperspirants from which the element usually enters into the human body. Evidence for the neurotoxicity of Al is described in various studies, but still the exact mechanism of Al toxicity is not known. However, the evidence suggests that the Al can potentiate oxidative stress and inflammatory events and finally leads to cell death.

Al is considered as a well-established neurotoxin and have a link between the exposure and development of neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (ALS), Alzheimer's disease (AD), dementia, Gulf war syndrome and Parkinsonism. Here, we review the detailed possible pathogenesis of Al neurotoxicity. This review summarizes Al induced events likewise oxidative stress, cell mediated toxicity, apoptosis, inflammatory events in the brain, glutamate toxicity, effects on calcium homeostasis, gene expression and Al induced Neurofibrillary tangle (NFT) formation. Apart from these we also discussed animal models that are commonly used for Al induced neurotoxicity and neurodegeneration studies. These models help to find out a better way to treat and prevent the progression in Al induced neurodegenerative diseases.

Contents

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1. Introduction

Al, the third most abundant element and the most common metal in the earth's crust and it is ubiquitous in the environment. Al toxicity only happens when exposure to an extremely high level of Al content and it is unavoidable. Al enters into the human body through drinking water, food, use of utensils, deodorants, and drugs [1]. It is estimated that the dietary intake of Al can be from 3 to 30 mg/day [2]. Most of the Al compounds are relatively insoluble at physiological pH, limiting absorption of Al through ingestion or inhalation (only 0.06% to 0.1% absorbed). Al toxicity results due to an exposure to large amounts of Al containing compounds or direct inoculation of Al via dialysates, parenteral nutrition, or implanted foreign materials, such as surgical cements. In the brain Al accumulates in the sensitive area such as hippocampus and frontal cortex and is considered as a contributing factor in the pathogenesis of neurodegenerative diseases [1].

Normally Al has no known physiological role. The toxic consequences of Al exposure are thought to be related to dysregulation of other essential metals or ions; deposition of insoluble Al precipitates in vulnerable tissues; or proteins, lipids, or nucleotic interactions resulting in conformational and structural alterations, aggregation, and functional alterations. Neurological consequences of toxic Al exposure include Encephalopathy, Seizures, Motor neuron degeneration, Parkinsonism and death. Al mediated neurodegeneration resulting in cognitive dysfunction has been associated with elevated amyloid precursor protein (APP) expression [3,4], amyloid β (Aβ) deposition [5,6], impaired cholinergic projections and apoptotic neuronal death [7–9].

Al toxicity generally caused by the disruption of homeostasis of metals such as magnesium, calcium, and iron: in fact, Al mimics these metals in their biological functions and triggers many biochemical alterations [10]. Al exerts direct genotoxicity in primary human neuronal cells and induces neurodegeneration, through an increase in iron accumulation and oxygen reactive species (ROS) production [11]. Al induces neurotoxicity primarily by triggering oxidative stress that affects a large number of signaling cascades and ultimately causes cellular death. Al induced oxidative damage to DNA has been previously associated with neurodegeneration in different regions of the rat brain [12]. Most of the studies suggests that the removal of toxic metal from human body can represent a useful tool to avoid the beginning or progression of many diseases related to metal intoxication [13].

2. Aluminium-induced oxidative stress

Al chloride accelerates iron mediated lipid peroxidation (LPO) and the results marked oxidative damage by increasing the redox active iron concentration in the brain. Increased Oxy-radicals and loss of cellular homeostasis cause oxidative stress that leads to neurotoxicity [14]. The oxidative products released in the neurons are malondialdehyde, carbonyls, peroxynitriles, nitrotyrosines, and enzymes like super oxide dismutase (SOD), haemoxygenase-I, etc. [15]. The imbalance in oxidative oxidant-antioxidant status mainly characterized by increased LPO and a decreased level of antioxidant enzymes. Al chloride can able to react with superoxide anions, which are more potent oxidants. Al levels and its relation to oxidative stress has been reported in glia, astrocytes and microglia [16].

Primarily under oxidative stress conditions, SOD act as a first line defense against superoxide as it converts the superoxide anion to hydrogen peroxide (H_2O_2) and oxygen (O_2). It can also detoxify superoxide radical to H_2O_2, which is then converted to H_2O by catalase (CAT) at the expenditure of reduces glutathione (GSH). Glutathione in its reduced form is the most abundant intracellular antioxidant and is involved in the direct scavenging of free radicals or serving as a substrate for the glutathione peroxidase enzyme that catalyzes the detoxification of H_2O_2 [17]. Glutathione-s-transferase (GST) also helps in the detoxification of ROS by maintaining a metabolic intermediate such as GSH [14].

Al alters the cellular redox state by inhibiting the enzymes involved in antioxidant defense which functions as blockers of free radical processes. There will be a significant decreased in the activities of SOD in cerebrum, cerebral hemisphere and brain stem after Al exposure [18]. Al can bind to negatively charged brain phospholipids, which contain polyunsaturated fatty acids and are

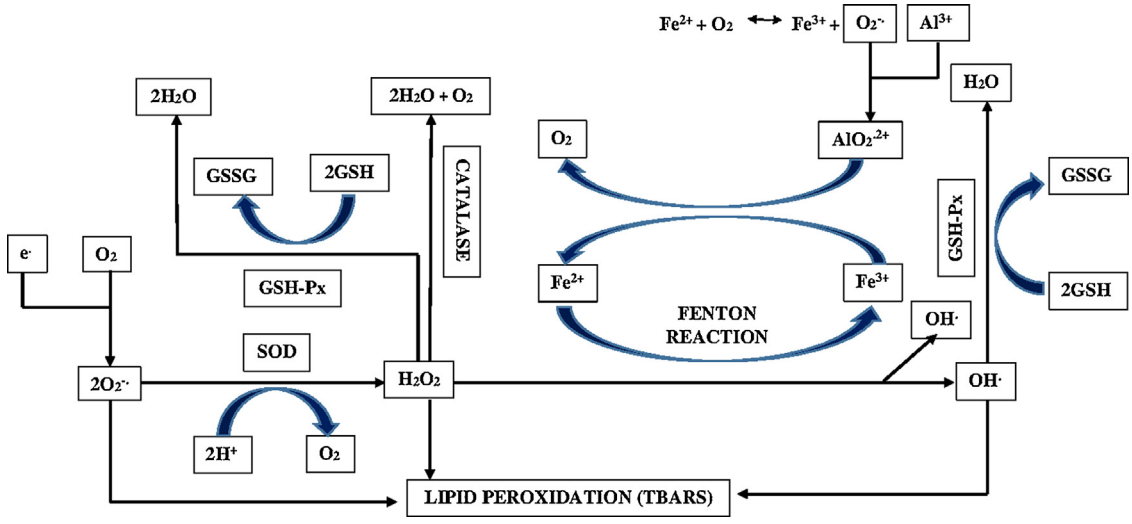

Fig. 1. Diagrammatic representation of aluminium, ROS, anti-oxidative enzymes and lipid peroxidation. TBARS—Thiobarbituric acid reactive substances, SOD—Superoxide dismutase, GPx—Glutathione peroxidase, GSSG—Oxidized glutathione.
Adapted from the research findings of Exley [20]; Halliwell and Gutteridge [23]).