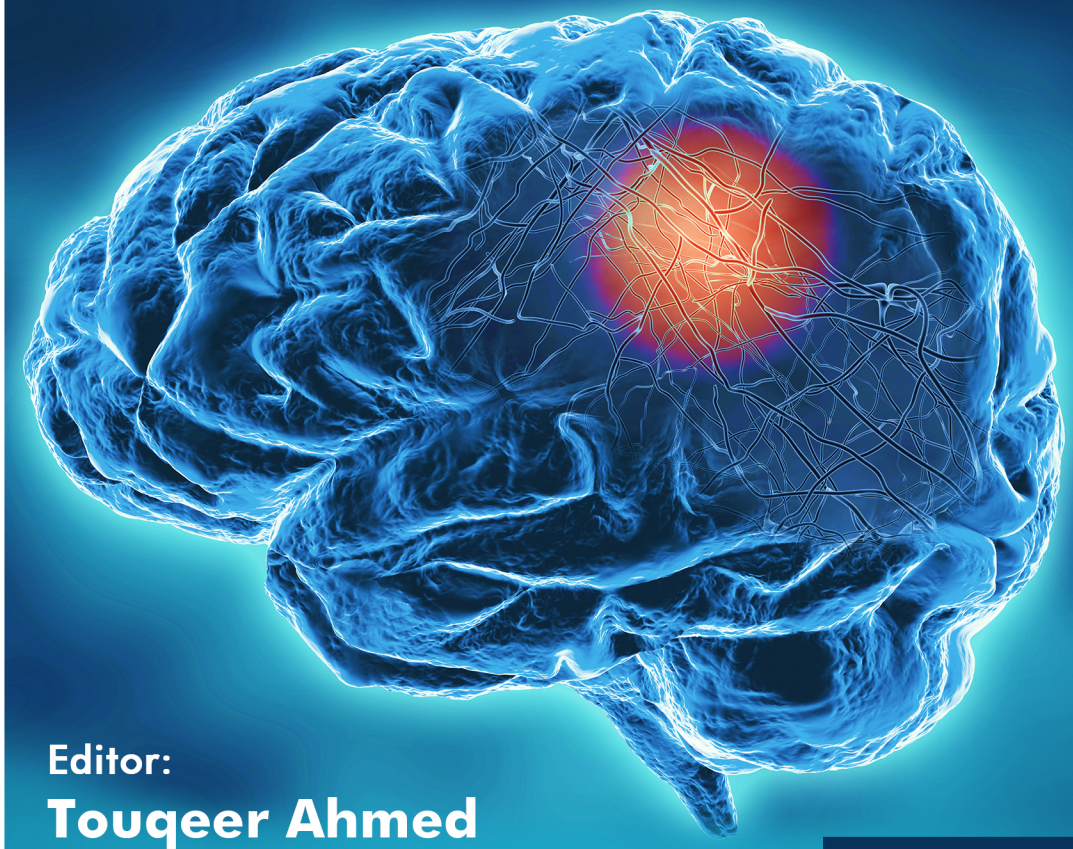
BIOCHEMICAL MECHANISMS OF ALUMINIUM INDUCED NEUROLOGICAL DISORDERS



Editor:
Touqeer Ahmed

Bentham Books

Biochemical Mechanisms of Aluminium Induced Neurological Disorders

Edited by

Touqeer Ahmed
Department of Healthcare Biotechnology
Atta-ur-Rahman School of Applied Biosciences
National University of Sciences and Technology
Islamabad, Pakistan

Biochemical Mechanisms of Aluminium Induced Neurological Disorders

Editor: Touqeer Ahmed

ISBN (Online): 978-1-68108-883-9

ISBN (Print): 978-1-68108-884-6

ISBN (Paperback): 978-1-68108-885-3

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Ltd.
Executive Suite Y - 2
PO Box 7917, Saif Zone
Sharjah, U.A.E.
Email: subscriptions@benthamscience.net

CONTENTS

PREFACE

This book "Biochemical Mechanisms of Aluminium Induced Neurological Disorders" is composed of six chapters contributed by reputed scientists working in the field of metals neurotoxicity and studying the role of metals on various neurological disorders. The salient features of this book which make it unique are– it highlights the basic as well as clinical mechanisms of metals induced neurotoxicity in various neurological disorders, and another unique feature of this book is that it discusses the role of Aluminium induced neurological disorders, alone and in combination with other toxic metals as well as with the high fat diet intake, thus adding diversity and unraveling new features of metals neurotoxicity in real scenarios.

Aluminium is present in the earth's crust and it is a well known environmental toxin/metal which has been found to be associated with various neurological disorders. Aluminium has been found to be a very strong risk factor for the development of Alzheimer's disease. It is known to cause neurotoxicity by various mechanisms, which are highlighted in this book. Cholinergic system impairment seems to be prominent; however, other mechanisms and pathways are also discussed and elaborated in this book. This book also covers missing aspects of the blood brain barrier and developmental toxicity, which are not very well studied areas related to Aluminium exposure alone or in combination with other metals. Knowing the pharmacokinetics of Aluminium and other metals are important aspects that can help us to understand the exposure of metals and their brain entry mechanisms, thus, opening up new horizons for the development of therapeutic options. Finally, I would say that this comprehensive book is well balanced and well written in developing understandings of basic and clinical mechanisms of Aluminium induced neurological disorders.

Touqeer Ahmed
Department of Healthcare Biotechnology
Atta-ur-Rahman School of Applied Biosciences
National University of Sciences and Technology
Islamabad, Pakistan

List of Contributors

Abida Zulfiqar	Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad 44000, Pakistan
Amna Liaqat	Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad 44000, Pakistan
Armeen Hameed	Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad 44000, Pakistan
Fatima Javed Mirza	Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad 44000, Pakistan
Ghazal Iqbal	Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad 44000, Pakistan
Laraib Liaquat	Multidisciplinary Research Lab, Bahria University Medical and Dental College, Bahria University, Karachi, Pakistan
Rida Nisar	HEJ Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan
Saadia Zahid	Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad 44000, Pakistan
Saida Haider	Neurochemistry and Biochemical Neuropharmacology Research Unit, Department of Biochemistry, University of Karachi, Karachi, Pakistan
Sanila Amber	Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad 44000, Pakistan
Sara Ishaq	Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad 44000, Pakistan
Syeda Mehpara Farhat	Department of Biological Sciences, National University of Medical Sciences, Rawalpindi-46000, Pakistan
Touqeer Ahmed	Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad 44000, Pakistan
Tuba Sharf Batool	Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad, Pakistan
Zehra Batool	Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan

CHAPTER 1

Biochemical Mechanisms of Aluminium and Other Metals Exposure, Their Brain Entry Mechanisms, Effects on Blood Brain Barrier and Important Pharmacokinetic Parameters in Neurological Disorders

Sara Ishaq[1], Amna Liaqat[1], Armeen Hameed[1] and **Touqeer Ahmed[1,*]**

[1] Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad 44000, Pakistan

Abstract: Evolution of life has resulted in a strong association between environmental metals and the biological processes taking place in the human body. Some of these metals are essential for the survival of human life, while many others can pose harmful effects on the body if exposed continuously. These toxic metals include Aluminium (Al), Arsenic (As), Lead (Pb), Mercury (Hg), Cadmium (Cd) etc. Upon entry into the brain, these metals lead to the development of many neurological disorders by increasing the levels of ROS, disturbing calcium ion efflux, causing mitochondrial dysfunction and activating an immunogenic response. These metals also cause a decrease in the levels of certain antioxidants in the brain like glutathione, superoxide dismutase and catalase. Moreover, the decrease in the level of certain genes like brain derived neurotropic factor (BDNF) due to metals neurotoxicity can also cause depletion of the memory and other cognitive functions leading to many neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), etc. The following chapter explains the pharmacokinetic mechanisms involved in metals induced neurotoxicity leading to different neurological disorders.

Keywords: Neurodegeneration, Metals Accumulation, Metals Toxicity, Metals Pharmacokinetics, Metals Distribution.

[*] **Correspondence author Touqeer Ahmed PhD**: Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad- 44000, Pakistan; Tel: +92-51-9085-6141, Fax: +92-51-9085-6102;
E-mail: touqeer.ahmed@asab.nust.edu.pk

INTRODUCTION

Metals and their Evolution in Biological Processes

Metals have been associated with biological systems for billions of years and this association has also been known to evolve with time. Many life processes include a variety of naturally occurring metal complexes in different ways [1]. Major metals like iron, zinc, magnesium, manganese etc. and minor metal ions like copper, nickel, cobalt, molybdenum, tungsten, etc., have been incorporated into the living organisms by the interplay of their metabolic pathways with the products of biogeochemical weathering [2]. Organisms are now able to adapt or die due to the natural development of these metals and other chemicals. Many important life processes of current organisms especially, the metabolic processes require redox reactions which are dependent on the presence of these metals as they have a tendency to lose or gain electrons [3].

Metals are so central in the cellular processes that almost 30% of the overall body proteins are metallo-proteins. Almost 40% of all enzymatic reactions require metals and at least one step of all the biological pathways involve a metal [4]. For example, calcium is not only required for strong bones and teeth but is also involved in reducing muscle cramps and triggering a number of cellular processes. Similarly, many of the cellular activities are dependent on magnesium which is the most abundant element inside the cells after potassium. The biological processes taking place in the nucleus involve metals like calcium, magnesium, copper, zinc, iron and manganese which are present there, in detectable amounts, *i.e.*, 10^{-2}-10^{-4}mol. These metals bind to the DNA and RNA in the cells, even RNA's active configuration is also dependent upon the concentrations of magnesium and manganese [5]. Magnesium is also responsible for providing energy to millions of cells in the animal and plant bodies by the activation of the production of ATP. It is also involved in some other processes like the process of DNA polymer synthesis along with other divalent metal ions like zinc and manganese [6]. Some of the important functions of all of these metals are given in Table **1** in detail. Thus, the metals are considered to be essential for the biological system as without them the system may collapse.

Table 1. Some of the important functions of essential metals and their related deficiency problems inside the body.

Metals		Important Biological Functions	Deficiency Issues	References
Major Essential Metals	**Calcium (Ca2+)**	• Provides strength to bones and teeth • Involved as a second messenger in signal transduction pathways like neurotransmitter release, muscle contraction, fertilization, hormonal release etc. • Acts as enzymes cofactor • Involved in blood coagulation process • Maintains potential difference across excitable cell membranes	• Seizures • Depression • Dental Problems • Osteopenia and Osteoporosis • Various skin conditions • Painful premenstrual syndrome • Chronic joint and muscle pain • Bones weaknesses and fractures • Muscular disability	[7-10]
	Sodium (Na+)	• Maintains blood, plasma and other body fluids' homeostasis • Involved in signal transduction of the central nervous system by controlling renin- angiotensin system and atrial natriuretic peptide • Involved in the transport of solutes across cell membranes via Na2+/K+ pump • Involved in body's buffer system via Na2+/K+ pump	• Headache • Confusion • Seizures • Nausea and vomiting • Muscles weakness, spasms or cramps • Muscular irritability and restlessness • Loss of energy, drowsiness and fatigue • Coma	[11-13]
	Potassium (K+)	• Involved in electrolyte metabolism along with sodium and chloride ions • Help in conduction of nerve impulses • Acts as a cofactor of enzymes • Controls the transport of essential elements via Na2+/K+ pumps • Involved in electrical signaling via potassium channels	• Muscle paralysis • Cardiac arrhythmias • Mood disorders • Tingling and numbness in hands and feet • Breathing difficulties • Weakness and fatigue • Muscles cramps and spasms • Digestive problems	[12, 14, 15]

CHAPTER 2

Co-Exposure of Aluminium with other Metals Causes Neurotoxicity and Neurodegeneration

Abida Zulfiqar[1], Ghazal Iqbal[1] and **Touqeer Ahmed[1,*]**

[1] Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad 44000, Pakistan

Abstract: Metals are key players in maintaining and regulating gene expression, antioxidant response, cell structure and neurotransmission. Their presence in the human body is required in trace amounts to perform these functions, however, excessive accumulation of these metals in various organs, including the brain, leads to detrimental neurological consequences by altering oxidative stress, protein misfolding, mitochondrial dysfunction, DNA fragmentation and apoptosis. These events over a course of time contribute to mild cognitive impairment, movement related disorders, learning and memory deficits which can further progress to neurodegeneration. According to some epidemiological and clinical findings, there is strong evidence of metal exposure and its correlation with a number of neurological diseases like Alzheimer's diseases (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), Guillain-Barre disease (GBD), Parkinson's disease (PD) and multiple sclerosis (MS), etc. Moreover, metal ions tend to exacerbate the accumulation of neurotic plaques in AD associated pathologies. It has been observed that metals like iron, zinc, copper and Aluminium are elevated in AD brains, causing damage to the synapses. Such metal ions imbalances are associated with aging related neuropathies and disease progression. Some other factors contributing to neurodegeneration include predisposition to ApoE allele, the interaction and synergistic effect of multiple metals together, the impact of cholesterol, amyloid precursor protein (APP) processing, and increased total tau along with Aβ production play a key role in increased biosynthesis of reactive oxygen species in the brain. Such events tend to reduce neuronal viability and function, thus causing cognitive decline.

Keywords: Metals, Mild cognitive Impairment, Neurodegeneration, Neurotoxi city.

[*] **Corresponding author Touqeer Ahmed:** Neurobiology Laboratory, Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Sector H-12, Islamabad - 44000, Pakistan; Tel:+ 92-51-9085-6141, Fax:+ 92-51-9085-6102; E-mail: touqeer.ahmed@asab.nust.edu.pk

Touqeer Ahmed (Ed.)

1. ACCUMULATION OF METALS IN THE BRAIN AND COGNITIVE IMPAIRMENT

Cognitive impairment is a collective term used when a person's cognitive functions are compromised. There is an overall deficit in learning and memory because such people have difficulty in remembering things, their language, visuospatial abilities are also impaired [1]. This altogether accounts for an increased disability risk along with substantial costs of health care [2]. Cognitive functions are also affected by other factors like environment, genetics, food consumption/diet, life style and aging [3]. With aging, a decline in cognitive functions is inevitable. This is mostly related to an overall increase in oxidative stress and abnormal aggregation of proteins [4]. Moreover, there are other risk factors that can accelerate the process of aging, these include smoking, alcohol consumption, depression, a western or high fat diet, pollution etc [5]. The cognitive deficit is increasing on a global level and it is expected to increase significantly more in developing countries. Along with these above mentioned factors, exposure to other neurotoxins cause increased oxidative stress and affects cognitive functions which then leads to irreversible neurodegeneration [6].

One of the most important risk factors for cognitive decline is exposure to heavy metals from the environment. The human body cannot synthesize or destroy metals. Therefore, in order to provide essential trace elements such as Copper (Cu) and Zinc (Zn) to the body, there are efficient mechanisms for transport, absorption and cellular uptake. Mostly heavy metals utilize this mechanism of transport to enter and accumulate in the various organs in the body [7]. These accumulated metals start the production of reactive oxygen species (nitric oxide and superoxide) in the biological system and result in a surge in oxidative stress. Increased reactive oxygen species (ROS) induce various DNA damages, protein modifications and lipid peroxidation resulting in neurotoxicity and neurodegeneration [8]. Oxidative stress worsens the cognitive abilities by damaging the functions of endothelial cells and invasion of macrophages to the brain parenchyma resulting in disruption of the blood brain barrier. This results in deficit of nutrients in brain cells and as a consequence neuroinflammatory processes begin [9]. Table **1** shows that how elevated levels of some metals can cause certain disorders.

Table 1. Elevated levels of heavy metals and different diseases associated along with their permissible limits.

Metal	Environmental Sources	Diseases Associated with Higher Metal Levels	Nervous System and Related Disorders	Permissible Limits of Metals in Body*	Safe Intake Quantities of Metal in Drinking Water*
Cu	Meat, fish [10]	Bone disorder [11], hepatitis [12], cancer, cardiovascular disease [13]	Motor neuron diseases [14], Alzheimer's disease [15]	0.1 mg/L 0.5µg/kg	1ppm
Al	Beverages can and foil, cosmetics, antiperspirants, antacids and water treatment plants [16]	Ischemic heart disease [17], chronic kidney disease [18], pulmonary dysfunction [19]	Alzheimer's disease [20], Parkinson's disease [21], dementia [22]	0.1µg/kg	0.1ppm
Zn	Food [23], zinc fumes, soil [24], Refineries.	Cancer, cardiovascular disease [13], diabetes mellitus.	Alzheimer's Disease [25]	15mg/L 1mg/kg	5ppm
Pb	Contaminated food, lead containing paint, drinking-water, lead-glazed material for food storage and petrol.	Developmental disabilities [26]	Neurotoxicity, attention deficit hyperactivity disorder, risk of developing mild mental retardation and lead encephalopathy [26, 27]	0.1mg/L 25µg/kg	0.05ppm
Mn	Diet, drinking water [28], metal laden dust in industrial areas [29]	Anemia [30], diabetes mellitus [31]	Parkinson's disease [32], neurotoxicity [33]	0.26mg/L 0.06mg/kg	0.4ppm
Cd	Color pigment present in paints, fertilizers, fabrication of nickel-cadmium batteries, anticorrosive agent, stabilizer in PVC products, tobacco smoking, and used as neutron-absorber in nuclear power plants [34].	Kidney damage, disturbed calcium and phosphorus metabolism, a possible higher risk of kidney stones [35], bone damage [36] and cancer [37].	Motor neuron disease, *e.g.* Amyotrophic lateral sclerosis [38]	0.06mg/L 7µg/kg	0.005ppm

ppm part per million, µg/kg = microgram per kilogram, mg/L = milligram per liter; *(World Health Organization, 2008).

CHAPTER 3

Role of aluminium in Post-Translational Modifications and Neurological Disorders

Saadia Zahid[1,*], **Sanila Amber**[1] and **Fatima Javed Mirza**[1]

[1] *Neurobiology Laboratory, Atta ur Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad, Pakistan*

Abstract: Increased exposure or elevated levels of aluminium(Al) in humans cause various detrimental pathological processes especially affecting the central nervous system. Al-induced neurotoxicity predominantly leads to impaired motor coordination, cognition and learning and memory deficits. Significant association of chronic Al exposure with several neurological disorders, including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) Parkinson's disease (PD) and multiple sclerosis (MS) is evident where it instigates aberrant expression of various proteins *via* alterations in post-translational modifications (PTMs). In depth understanding of mechanism of action of Al, effect of altered PTMs and their detection methods is essential to revert anomalies induced by Al in these neurological disorders. The present chapter will attempt to summarize the role of Al in modulation of significant PTMs including phosphorylation, methylation, oxidation, ubiquitination and provide insights into its involvement in various neurological disorders.

Keywords: Aluminium, Alzheimer's Disease, Amyotrophic lateral Sclerosis, Multiple Sclerosis, Parkinson's Disease, Post-Translational Modifications.

INTRODUCTION

Aluminium (Al) is a highly abundant metal in the earth's crust and has been in use by mankind for centuries. It is widely utilized for food preservation, cans, kitchen utensils, and vaccine adjuvants, *etc*. Because of its widespread availability, both in environment and foodstuff, human exposure is almost unavoidable. Increased exposure or elevated levels of Al in humans may cause various detrimental pathological processes especially affecting the central nervous system (CNS). Elevated levels of Al in the brain are associated with mitochondrial dysfunction,

[*] **Corresponding author Saadia Zahid**: Neurobiology Laboratory, Atta ur Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad, Pakistan; Tel:+92 51 90856159;
E-mail: saadia.zahid@asab.nust.edu.pk

Touqeer Ahmed (Ed.)

apoptosis, lipid peroxidation, oxidative stress, protein misfolding, and neurotoxicity leading to neurodegeneration (Fig. **1**).

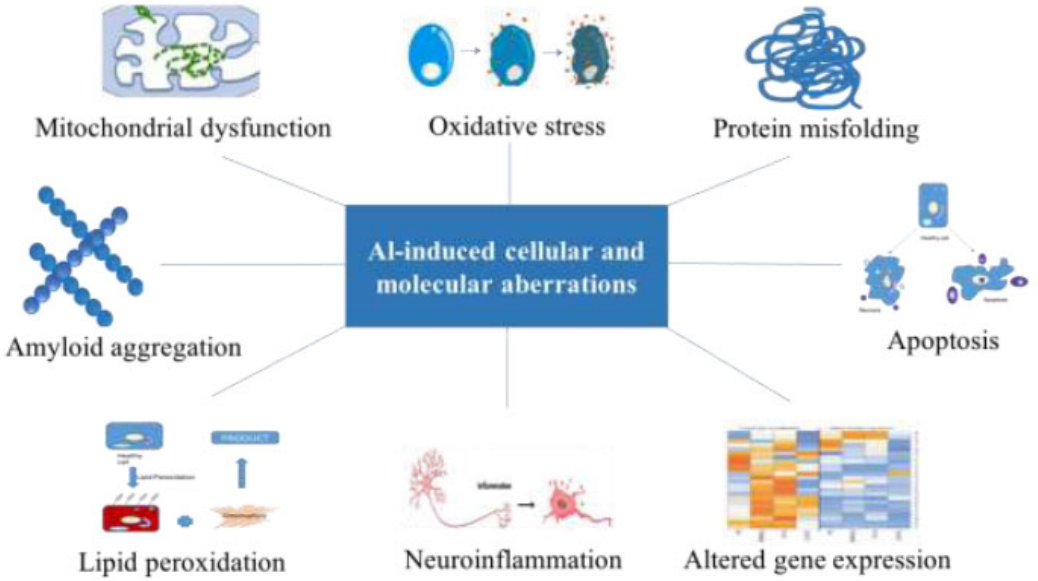


Fig. (1). Diagrammatic representation of Aluminium-induced cellular and molecular aberrations.

1. ALUMINIUM MEDIATED OXIDATIVE STRESS

Although oxygen is essential for the survival of living organisms and serves to meet the energy needs of the biological tissues, it produces an increase in the levels of free radicals, resulting in toxic effects on the tissue. Hyperoxia and the deteriorative effects of reactive oxygen species (ROS) have also been attributed to neurotoxicity as brain tissues have a high consumption rate of oxygen and low activity of antioxidant enzymes. Partially reduced forms of oxygen or ROS exist in different varieties, including hydrogen peroxide (H_2O_2), superoxide ($O_2^{\cdot}$) and the hydroxyl radical (OH•) and react with the biological molecules altering their function and causing cell damage and death [1]. Oxidative stress occurs as a consequence of increased ROS brought about by an imbalance in the production of ROS and the levels of antioxidants, ultimately affecting the cells adversely. It has been implicated in various neurological disorders including Alzheimer's disease (AD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) [2].

Al, despite its low redox potential, causes oxidative damage through various mechanisms. It binds to the negatively charged phospholipids containing polyunsaturated fatty acids in the neuronal cell membranes rendering them more susceptible to the effect of ROS. It also causes the production of ROS and Fe^{3+} through the stimulation of iron-initiated lipid peroxidation in the Fenton reaction. Additionally, it raises the oxidative capacity of superoxide ($O_2^{\cdot-}$) by neutralizing it to form an Al-$O_2^{\cdot-}$ complex [3].

Numerous studies conducted on animal models have revealed that prolonged exposure to Al has resulted in oxidative damage that was more evident in the prefrontal cortex, cerebellum, hippocampus and brainstem. It was also found that, in addition to a significant increase in lipid peroxidation, Al also declines the cellular levels of antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase and transferase. A sharp decrease in the mitochondrial activity is also associated with the detrimental oxidative damage induced by Al which causes disruption in the mitochondrial bioenergetics and reduces the respiratory efficiency and mitochondrial capacity [4].

2. ALUMINIUM INDUCED NEUROTOXICITY

Al exhibits neurotoxic effects which could be attributed to its high affinity to proteins and the ability to crosslink them [5]. An initial account of these neurotoxic effects was noticed in dialysis patients who were subjected to a dialysate enriched with Al salts. These patients not only exhibited increased concentrations of Al in the plasma and brain tissue but also showed symptoms of neurotoxicity like disorientation, memory loss which eventually led to dementia. Al also affects the hippocampal calcium signal pathways, thereby disrupting the neuronal plasticity and causing loss of memory and cognition [6].

3. ALUMINIUM AND NEUROLOGICAL DISORDERS

3.1. Aluminium and Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative disorder characterized by the formation of amyloid beta plaques (Aβ) and neurofibrillary tangles (NFTs) and manifested by the loss of memory and cognition. The possibility of a role of Al in AD arose in 1965 with the accidental finding of neuronal changes involving neurofibrillary degeneration in the brain of rabbits injected with Al salts [7]. The cholinotoxic activity of Al coupled with the promotion of apoptotic neuronal loss makes it a highly potent neurotoxin inducing neurodegeneration and loss of learning and memory.

CHAPTER 4

Effect of Aluminium on Synaptic Plasticity

Syeda Mehpara Farhat[1,*]

[1] *Department of Biological Sciences, National University of Medical Sciences, Rawalpindi-46000, Pakistan*

Abstract: Aluminium (Al) is the third most abundant metal in the earth's crust and it has long been associated with the pathogenesis of many neurological disorders. Recently, vast use of this metal in various industries and its elevated leaching from earth reservoirs, due to acid rain, has greatly increased human exposure to this metal. Due to the controversial nature of Al effects on the nervous system, it is important to thoroughly understand the effects of Al on neurological functions. This chapter is focused on understanding the effects of Al on the electrophysiological properties of neurons. The emphasis is on the effects of Al on synaptic plasticity, which is an important underlying mechanism in learning and memory, and voltage-gated ion channels. The evidence indicates that Al affects Long term potentiation (LTP), the most widely studied form of synaptic plasticity, *via* its effects on various signaling pathways.

Keywords: Aluminium, AMPA Receptor, Electrophysiological Variation, LTP, LTD, Metabotropic Glutamate Receptors, NMDA Receptor, Voltage-Gated Channel, Voltage dependent Calcium Channel, Neurotoxicity.

INTRODUCTION

Aluminium (Al) is the third most abundant element in the earth's crust and is a known neurotoxicant [1]. Al has been suggested to be neurotoxic based on different evidences from animal models, human studies and cell culture studies [2, 3]. Al gets easy access to the human body due to its addition to water purification systems, vaccine adjuvants and cosmetics [4, 5]. Al is also used as an additive in processed food [6]. Once in the body, Al is reported to cause damage to the blood brain barrier [7] and gets access to the brain *via* transferrin receptors and accumulates in the cortex and hippocampus [8]. The neurons are predisposed to toxic effects of Al accumulation due to their long life span [9]. The neurotoxic potential of Al has been reported in several studies and has been linked to various

[*] **Corresponding author Syeda Mehpara Farhat**: Department of Biological Sciences, National University of Medical Sciences, Rawalpindi-46000, Pakistan; Tel:??????; E-mail: mahpara.farhat@numspak.edu.pk

Touqeer Ahmed (Ed.)

neurodegenerative disorders, including multiple sclerosis [10], dialysis dementia [11], Parkinson's disease and Alzheimer's disease [12]. Although the causative role of Al in neurodegenerative disorders is controversial but common consensus is that Al may exacerbate the underlying events associated with neurodegenerative disorders [13].

Various studies on animal models have shown that, through its neurotoxic mechanisms, Al causes learning and memory deficits [14, 15]. The learning-related cellular changes might be either due to modifications at synapses or changes in the intrinsic properties of neurons [16] that may cause a decline in synaptic plasticity [17]. Synaptic plasticity refers to the changes in the strength of synaptic responses according to the neuronal activity [18] and it is the underlying process in memory formation *via* conversion of transient experiences to persistent memory [19].

Due to its positive oxidation state Al^{+3} has great affinity towards oxygen donors having a negative charge [16]. Therefore, the binding of Al to receptors and enzymes involved in neurotransmitter synthesis might affect neurotransmitter systems [20 - 22] and consequently result in synaptic plasticity impairment. These properties of Al cause neurotoxicity, leading to neurodegeneration and consequently learning and memory deficits [19]. The ability of Al to cause learning and memory deficits *via* its effects on synaptic plasticity has been known for more than two decades [23, 24] and is discussed in this chapter.

Effects of Al Accumulation on Synaptic Plasticity

With an increase or decrease in synaptic activity, the connections between neurons may strengthen or weaken. This change in the strength of the connection between neurons is referred to as synaptic plasticity [18]. The enhancement in the strength of synapses, in response to neuronal stimulation is referred to as long term potentiation (LTP), whereas the reduction in synaptic strength is termed as long term depression (LTD). Synaptic plasticity is a basic neural mechanism of learning and memory, which are the main functions that deteriorate due to Al accumulation in the brain. Al exposure is reported to affect both the early phase LTP, which is protein synthesis independent [25], and late phase LTP, which requires new protein synthesis, in the CA1 region of the hippocampus [26]. Al administration affects LTP, both *in vivo* and *in vitro*, in a concentration dependent manner [23]. Similarly, from the recordings performed on the dentate gyrus of hippocampus, it was observed that Al administration affects LTD along with LTP in neonatal rats [27] and in adult rats [28]. Al administration is also known to inhibit induction of tetra-ethyl ammonium (TEA)-induced synaptic enhancement of LTP, in a concentration and time dependent manner [24]. TEA is a potassium

(K^{+2}) channel blocker and is frequently used to study the mechanism of LTP, induced by electrical stimulation of afferent fibers [24]. These inhibitory effects of Al might be due to inhibition of Ca^{+2} conduction, which might interfere with Ca^{+2} dependent processes [24]. Moreover, the Al-induced impairment in synaptic plasticity might be due to increased apoptosis of hippocampal neurons [25].

Effect of Al on Ca^{+2} Channel and Ca^{+2} Signaling

During the development of synaptic plasticity, strong depolarization currents result in a higher influx of Ca^{+2} ions in the postsynaptic neuron. This Ca^{+2} ion completely displaces the Mg^{+2} ion, which blocks N-methyl-D-aspartate receptor (NMDAR), and this results in LTP induction *via* NMDAR activation. Weak depolarization of postsynaptic neuron leads to entry of a smaller amount of Ca^{+2} inside the cell and, therefore, partial replacement of Mg^{+2} ion, which leads to LTD induction. Thus the entry of Ca^{+2} into the cell is crucial for the induction of both LTP and LTD [29]. The voltage-dependent calcium channels (VDCC) are of prime importance because Ca^{+2} influx through these channels leads to activation of various events that result in the release of neurotransmitter glutamate from the presynaptic cells. This neurotransmitter consequently activates NMDAR and metabotropic glutamate receptor (mGluR) on postsynaptic cells for induction of LTP or LTD [16]. The Al inhibits Ca^{+2} influx through these channels [30], which leads to a reduction in the voltage-activated calcium channel current [31]. Moreover, due to the important role of mitochondria in the regulation of synaptic plasticity [32], irreversible inhibition of mitochondrial voltage-gated channel (VDAC) permeability by the micromolar quantity of Al [33], may also contribute to Al-induced synaptic plasticity inhibition. Furthermore, Al is also reported to affect high voltage activated (I_{HVA}) Ca^{+2} channels [34]. This effect of Al on Ca^{+2} channels might be due to the interaction of Al with binding sites within and outside these channels [31]. But these effects of Al on Ca^{+2} channels are not ubiquitous but different Al compounds act differently on these channels [35]. Moreover, the blockade of Ca^{+2} channels with Al is pH dependent and the extent of blockade increased with reduction in pH [36]. The application of Al is also reported to shift the current-voltage relationship towards depolarized voltage in cultured rat dorsal root ganglion neurons. But, this shift is Al concentration dependent and the magnitude varies in different cells [36]. The impairment in synaptic transmission has been observed due to inhibitory action of Al on voltage-gated Ca^{+2} channels [37]. Furthermore, Al acts as an antagonist of the enzymes containing Ca^{+2} and Mg^{+2} as these ions are replaced by Al and, therefore, the activity of Ca^{+2} dependent protein kinases is inhibited [38]. Thus the deficits in Ca^{+2} signaling might be the reason for Al induced learning and memory deterioration [39].

CHAPTER 5

Aluminium and other Metals Exposure Cause Neurological Disorders: Evidence from Clinical/ human Studies

Zehra Batool[1], Laraib Liaquat[2], Tuba Sharf Batool[3], Rida Nisar[4] and **Saida Haider[5,*]**

[1] *Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan*

[2] *Multidisciplinary Research Lab, Bahria University Medical and Dental College, Bahria University, Karachi, Pakistan*

[3] *Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad, Pakistan*

[4] *HEJ Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan*

[5] *Neurochemistry and Biochemical Neuropharmacology Research Unit, Department of Biochemistry, University of Karachi, Karachi, Pakistan*

Abstract: Exposure to Aluminium and other heavy metals has become a serious concern in today's modern life. Due to excessive use and improper disposal of heavy metals, the entire food chain is being contaminated, which is imposing various health risks for humans and other living organisms. These heavy metals particularly induce oxidative stress through different mechanisms which can ultimately interfere with the normal physiological activities. Brain is highly prone to oxidative stress due to its rich polyunsaturated content and high oxygen consumption than the periphery. Therefore, emphasis has been given to neurotoxicological effects produced by exposure to heavy metals. In this regard, the effects of both essential and non-essential heavy metals have been investigated in various clinical studies which are demonstrating them as a serious threat to normal brain function. This chapter summarizes the neurotoxicological effects of heavy metals which have been revealed in various human studies.

Keywords: Clinical Studies, Heavy Metals, Neurological Disorders, Oxidative Stress, Toxicity Mechanism.

[*] **Corresponding author Dr. Saida Haider:** Neurochemistry and Biochemical Neuropharmacology Research Unit, Department of Biochemistry, University of Karachi, Karachi, Pakistan; Tel:+92-21-99261313-17;
E-mail: saida-h1@hotmail.com

Touqeer Ahmed (Ed.)

INTRODUCTION

Exposure to metals through various sources, including inhalation and ingestion, can result in accumulation in the body. Some of the metals have an essential role in the physiological and biochemical functions at an appropriate concentration. However, at higher concentrations they can accumulate in various vital organs of the body and can cause toxicity. These metals include chromium, cobalt, copper, iron, magnesium, manganese, molybdenum, nickel, selenium, and zinc. Toxic heavy metals having no known biological activities are considered hazardous metals since they can cause toxicity in the human body even at very low doses. All these metals can readily cross the blood brain barrier and can accumulate there, which may result in neurotoxicity. The mammalian nervous system becomes susceptible to metal-related redox damages as a consequence of several biochemical and physiological functions, including; high consumption of oxygen in neuronal cells as compared to the periphery, increased generation of reactive species due to reduced efficiency of mitochondria during aging, vulnerability to lipid peroxidation due to abundant content of unsaturated fats in the brain, the increased tendency of neurotransmitters to become oxidized and insufficiency of certain antioxidant mechanisms [1]. Metal-induced neurotoxicity is considered as one of the major reasons for neuronal injuries leading to neurological disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, autism spectrum disorders, Huntington's disease, multiple sclerosis, Wilson's disease, Guillain–Barré disease, and Gulf War syndrome. There are various mechanistic pathways through which metal can induce neurotoxicity, such as generation of reactive oxygen and nitrogen species, production of pro-inflammatory biomolecules, suppression of antioxidants, mitochondrial dysfunction and/or imbalance of calcium homeostasis. This chapter represents the clinical studies which have been done to demonstrate the neurological disorders induced by metal toxicity.

NEUROLOGICAL DISORDERS INDUCED BY HAZARDOUS METALS ALUMINIUM

Mechanism of Aluminium -Induced Neurotoxicity

Aluminium is associated with neurodegenerative disorders and other complications, including Alzheimer's disease, Parkinson's disease, amyotropic lateral sclerosis, multiple sclerosis, autism and epilepsy and in all these diseases Aluminium serves as a toxic co-factor. Aluminium enhances inflammatory processes in brain by various mechanisms such as by activation of microglia and by inducing pro-inflammatory gene expression. Exacerbation of inflammatory

processes is similar to those observed in neurodegenerative disorders such as Alzheimer's disease brain [1].

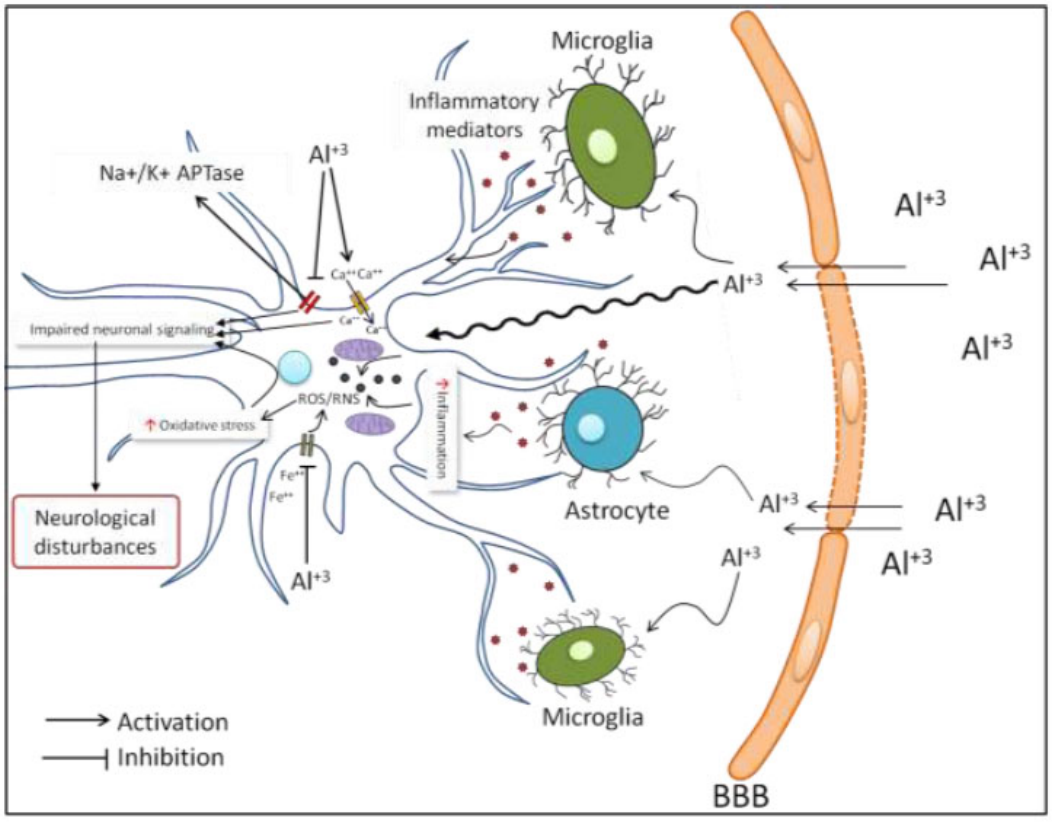


Fig. (1). Proposed mechanism of action of Aluminium-induced neurotoxicity. Refer to the text for detail. ROS: reactive oxygen species; RNS: reactive nitrogen species.

Alteration of nerve cells morphology is the most reported feature of Aluminium neurotoxicity following its exposure [2]. Permeability of blood brain barrier is compromised with age and as a result of this, substances that are confined to systemic circulation can enter the brain easily. With age, the cerebral levels of Aluminium increase and inside the brain, it expedites the aging process by oxidative alteration. As Aluminium enters the brain, it initiates the production of reactive oxygen species and activates glial cells; both of these pathways stimulate a chronic inflammatory response that eventually results in neurodegeneration [3]. Aluminium toxicity includes exacerbation of oxidative stress by increasing iron-driven and superoxide oxidation, by interfering transport and storage of iron, impairing antioxidant enzyme activities and increasing lipid peroxidation. It also disrupts calcium homeostasis, leading to a marked increase in intracellular

CHAPTER 6

Developmental Toxicity of Aluminium and other Metals: Areas Unexplored

Laraib Liaquat[1,2], Zehra Batool[3,*] and **Saida Haider[1]**

[1] *Neurochemistry and Biochemical Neuropharmacology Research Unit, Department of Biochemistry, University of Karachi, Karachi, Pakistan*

[2] *Multidisciplinary Research Lab, Bahria University Medical and Dental College, Bahria University, Karachi, Pakistan*

[3] *Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan*

Abstract: Reproduction and developmental damage has irreversible consequences compared to other body functions and may have adverse effects throughout life. In some circumstances, the damage passes from generation to generation. Many environmental agents contribute to developmental toxicities such as toxic metals, insecticides or pesticides, commercial or industrial pollutants, and air pollutants. Increased urbanization and industrialization have led to the accumulation of toxic metals in the environment. Widespread use of heavy metals in different fields such as agriculture, domestic, medical, industrial, and technological applications have resulted in increased exposure of heavy metals to the human population. Environmental exposure to heavy metals is extensively linked to toxic effects on mammalian embryos. Metals such as lead, cadmium, mercury and arsenic are known developmental toxicants that intensely affect fetal and embryonic development and cause certain malformations in developing embryo even at low concentrations. Other metals such as uranium, cobalt, lithium, Aluminium, manganese, and copper are also reported to induce developmental consequences, including neurobehavioral abnormalities, neural tube defects, fetal growth retardation, skeletal deformation, preterm or delayed birth, and still birth or postnatal death. Heavy metal developmental toxicity depends on different factors, including dose, duration, and route of exposure. Hence, heavy metals are known to be toxic to fetal and embryonic tissues and can produce serious teratogenicity in mammals; however, not much attention has been given to this topic. This chapter, therefore, summarizes the developmental toxicity of heavy metals on the mammalian system and their teratogenic mechanism in growing embryos.

Keywords: Developmental Toxicity, Heavy Metals, Toxicity Mechanism.

[*] **Corresponding author Zehra Batool**: Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan; Tel:+92-21-99261737; E-mail: xehra_batool@yahoo.com

Touqeer Ahmed (Ed.)

INTRODUCTION

Developmental toxicity is the science to understand the effects of environmental insults to interfere with the normal developmental process which may also result in adverse effects in the next generations. The genetic, nutritional, infectious, and chemical factors are thought to cause congenital abnormalities in humans. Such manifestations of developmental abnormalities have also been observed in animals. Exposure to heavy metals by different environmental factors particularly during the gestational process can induce deleterious and sometimes irreversible damages to the developing embryo. These effects may also result in further developmental abnormalities in the postnatal stage.

The conceptus, which is defined as the embryo and embryo-derived embryonic tissues, is highly susceptible to the toxic effects of heavy metals. These metals can cross the placenta and can directly interact with conceptus. The ultimate result of abnormal development may result in functional disorder, growth retardation, malformation, or death. Therefore, it is important to identify possible developmental toxicities of heavy metals that are commonly present in our environment. Most of the studies regarding metal toxicity have focused on the brain, hepatic, or kidney functions. However, little is known about the developmental toxicity induced by metals. Teratogenic agents act through a particular mechanism on developing cells and tissues to initiate embryogenic aberrations. The understanding of metal-induced defects in the placenta and fetal development is important to develop preventive and control approaches to ensure normal embryogenesis. In the following sections, teratogenic properties of those heavy metals have been explored with which the general population comes in contact almost on a daily basis.

ALUMINIUM

Aluminium is the third most abundant metal and constitutes about 8% of the earth's crust [1]. According to the World Health Organization's report, the living body gets exposed to Aluminium through food, antacids, cooking utensil, and deodorants besides occupational exposure such as defense-related factories, guns, and automobiles [2]. Aluminium compounds are also used in water purification processes that lead to increased Aluminium levels in drinking water. Aluminium compounds can reach systematic circulation *via* different routes such as dermal absorption, ingestion, and intramuscular injection [1].

Teratogenic Nature of Aluminium

Aluminium has the potential to cross the placental barrier and accumulate in fetal tissues [3]. Environmental and dietary exposure to Aluminium during the

maternal period causes developmental toxicities in mammals. Aluminium causes severe developmental syndromes, including neurodevelopment disturbances such as mental retardation, skeletal and soft tissue abnormalities, and growth retardation [4]. Oral exposure of a large amount of Aluminium to pregnant women is of special concern. Antacids are normally prescribed to pregnant women to treat dyspepsia and associated dyspeptic symptoms. Aluminium-containing antacids are associated with increased accumulation of Aluminium in maternal blood. Overexposure to Aluminium during pregnancy through antacids is linked with embryonic and fetal toxicities [5]. Therefore, due to toxicities associated with Aluminium exposure, it is generally suggested to limit the intake of Aluminium-containing antacids during pregnancy [6].

Aluminium exposure during the gestational period to female rats induces prenatal, teratogenic and postnatal adverse effects [7]. Studies have reported that Aluminium exposure can induce fetal abnormalities, growth retardation, delay in ossification in rats and mice [8]. Reported malformations are attributed to the transplacental passage of Aluminium [9]. Aluminium nitrate in mice induces abortions, preterm delivery, and fetal death. Aluminium-related developmental toxicities in animals depend on the route of administration and nature of Aluminium compound administered [6]. Oral administration of Aluminium chloride to female rats during organogenesis, fetal, and lactation period resulted in post implantation deaths, resorptions, morphological alterations along with the visceral and skeletal anomalies. Delayed birth, dystocia, neurobehavioral and respiratory disturbances are also observed following Aluminium exposure in animals during fetal development [7].

Mechanism of Teratogenic Activity

A number of possible mechanisms have been suggested regarding the teratogenic nature of Aluminium. Experimental work on Aluminium treated pregnant animals reported that Aluminium oral exposure during pregnancy alters tissue distribution of essential trace elements. Higher concentration of copper was found in the brain, whereas calcium, magnesium, manganese concentrations were significantly high in renal tissue. Such changes ultimately produce negative outcomes on fetal metabolism [10]. Aluminium competes with essential cations such as iron, calcium, and magnesium to bind with fluoride and phosphate anions. Such interactions alter the biological active mechanism of essential ions including uptake, distribution, and excretion [11]. Essential ions are required for proper bone formation; however, interactions of Aluminium with cations and anions produce fetal bone malformation [11]. It is also associated with inhibition of the parathyroid gland and osteoblast formation [12]. Aluminium accumulation in the fetal brain has negative consequences on neuronal cell nuclei where it interacts

SUBJECT INDEX

A

B

C

D

E

F

G

H

I

N

O

P

R

S

T

V

W

Touqeer Ahmed

Dr. Touqeer Ahmed has more than ten years of post-PhD experience in teaching, academics and doing research in pharmacology and neurosciences. He has served at various world reputed organizations such as, Brain Science Institute, Korea Institute of Sciences and Technology (KIST), South Korea and RIKEN Brain Science institute, Japan and currently serving at the National University of Sciences and Technology (NUST), Pakistan. He has served at key administrative positions such as Head of the Department and Head of Undergraduate program at NUST. He has outstanding teaching record and has won the best teacher award in 2017. He has also contributed significantly in research by publishing more than 50 journal articles and 4 book chapters, resulting in winning the best researcher award in 2018. Dr. Touqeer Ahmed has earned several honors. In 2004, Dr. Touqeer Ahmed was awarded certificate of the "best graduate of the history" at B. Pharmacy level. In 2020, he became the unique faculty member at ASAB NUST who won both the best teacher and the best researcher award. Dr. Touqeer Ahmed has shown interest to accept challenges to bring positive changes in the education system and society as a whole.