Metal accumulation studies

Metal ions play a crucial role in determining the health and disease status by influencing cellular biochemical pathways. Since the uptake mechanisms of the body are not able to distinguish between physiologically essential and harmful metals, the toxic metals absorbed consequently might interact and obstructs the normal functioning of the central nervous system (CNS), liver, kidney, and hematopoietic system, thus imposing a significant health hazard. Imbalances caused by essential metals or excess of toxic metals can lead to metabolic disorders and diseases. The degree of mineral accumulation within the body is considered as an important measurement index that can be used as a diagnostic tool for identification of clinical nutrition and disease state (Marshall, 2008).

Bioaccumulation of metal contaminants has the potential impact on living organisms. Metals can speciate in many ways and the speciation of metals in abiotic and biotic environmental media strongly influences their bioavailability and bioaccumulation. Bioaccumulation is a wide term used to describe the uptake of metal contaminant that is present in an easily available form whereby the body of organisms can uptake them from surrounding medium and accumulate in certain tissues.

Metal poisoning may be categorized into acute, sub-acute, sub-chronic and chronic based on the duration and frequency of exposure. Usually acute poisoning produces more serious rapid response which requires immediate medical attention. However, the sub-chronic exposure of animals to the metal may lead to chronic metal toxicities, may be defined as general ill health in which the metal reach the target sites and produce effects (Flora and Pachauri, 2010).
Aluminium can accumulate in the tissues of the human body. Since the use of aluminium cookware, aluminium-containing deodorants and other products are alarmingly increasing year by year in general population. The availability of this particular environmental metal contamination and its existence in easily absorbable form contributes to the increased levels of metal exposure (Ansari et al., 2004). However, the toxic metals cause different clinical conditions depending on the subjects, age, health, dose levels, route, and other conditions of metal exposure (Klaassen, 1996).

Aluminium, the toxic metal has been found to compete with essential metals in the metabolic reactions (Meiri et al., 1993) and also involved in oxidative stress mechanism leading to metal toxicity. The increased concentrations Al ions may lead to brain damage and then produce its toxic effects by inducing alterations in the normal functioning of the system, leading to neurodegenerative disorders such as Alzheimer’s disease (AD).

The chelation therapy can be used to prevent metal poisoning. Melatonin was found to reduce the toxic effects of metals by its chelating ability to bind to toxic metal ions to form stable complex structures. Melatonin has been shown to possess marked protective effects against the toxicity of various chemical toxicants including carcinogens and chemotherapeutic agents (Karbownik et al., 2001). Previous reports suggested that melatonin protection could be due to the inhibition of oxidative stress (Pal and Chatterjee, 2006; Reiter et al., 2000). Due to its anti-oxidant activity, small size, high lipophilicity and hydrophilicity, melatonin can easily penetrate the layer of biological membrane by passing between the hydrophilic heads of lipid molecules (Reiter et al., 2003). After exogenous administration, melatonin can easily cross various barriers and reach the brain
(Hardeland, 2005). The present investigation was carried out to study the variable vulnerability of different brain regions to Al toxicity and potential role of melatonin in combating the Al accumulation.

**Results**

In the present investigation brain Al levels were found to be 2.471, 0.878, 1.627 and 2.217 µg/ml in cerebral cortex, hippocampus, cerebellum and medulla oblongata of control mice respectively. The level of aluminium was found to be higher in cerebral cortex and least in hippocampus.

Cerebral cortex > Medulla oblongata > Cerebellum > Hippocampus

Aluminium exposure resulted in significant enhancement of Al accumulation levels in all brain regions. It was found to be 5.814 µg in cerebral cortex, 6.124 µg in hippocampus, 9.559 µg in cerebellum and 4.582 µg (Table 2.1 and Fig.2.1).

Cerebellum > Hippocampus > Cerebral cortex > Medulla oblongata

In mice administered with melatonin alone the aluminium levels in brain were less in concentration than in control mice group. It was recorded as 1.321 µg in cerebellum, 2.064 µg in cerebral cortex, 0.766 µg in hippocampus and 1.976 µg in medulla oblongata.

The Al levels, significantly reduced in group treated with both aluminium plus melatonin mice, when compared to Al treated mice. It was 2.802 µg in cerebral cortex, 0.848 µg in hippocampus, 2.793 µg in cerebellum and 2.571 µg in medulla oblongata. The relative level of Al accumulation was in the following order

Cerebral cortex > Cerebellum > Medulla oblongata > Hippocampus
Discussion

As aluminium is a non-essential metal its increased levels in brain may contribute to neurological disorders and also affects other functions of the body. Due to its toxic consequences, aluminium accumulation would certainly result in the decreased performance activity levels and same has been observed in albino mice treated with sub-chronic administration of aluminium acetate.

In the present study, aluminium levels of accumulation varied in different regions of the brain. This might be due to membrane selectivity and differential vulnerability of brain regions. In Al treated mice, the highest percentage increase in hippocampus (597%) over the control group was observed. This might be due to the potential increase in the permeability of the blood-brain barrier resulting in enhanced uptake of this toxic metal into the brain (Smith, 1990).

Aluminium is capable to accumulate within the body tissues (Agarwal et al., 1995). The toxicological effects of aluminium might depend on administration-route, the time and level of exposure (Yokel and McNamara, 2001; Abreo and Glass, 1993). Redhead et al. (1992) reported that intraperitoneal injection of aluminium adsorbed vaccines in mice caused a transient rise in brain tissue aluminium levels. The results obtained in the present study is in agreement with Mc Dermott et al. (1979), who reported that the hippocampus has the highest concentration of Al in the human brain, 6.5µg/g (dry weight) followed by frontal lobe and temporal lobe, while the corpus callosum has the lowest levels (1.5µg/g). Aluminium is found to be extremely neurotoxic and at high levels it was reported to result in inhibition of pre-natal and post-natal development of the brain (Yumoto et al., 2001). Golub et al. (1995) evidenced that even low-level exposure to Al$^{3+}$
during development and early adulthood in mice affected neurobehavioural parameters and reduced other trace element concentrations in the central nervous system. Bishop et al. (1997) reported that in infants receiving intravenous feeding with solutions containing aluminium resulted in neurological impairment.

Several investigators have studied that co-administration of Al with citrate, lactate or acetate increases Al levels in a variety of organs including brain. Numerous experimental protocols have demonstrated that Al can accumulate in hippocampus and cortex (Struys-Ponsar et al., 1997).

Yumoto et al. (2003) found that \(^{26}\)Al subcutaneously injected into lactating rats accumulated in different brain regions such as cerebrum, cerebellum, hippocampus, brain stem and spinal cord of suckling rats through maternal milk. Aluminium incorporated into these CNS regions of suckling rats via milk could not only inhibit the postnatal development of these tissues but also impair physiological functions of the tissues throughout their life times. Exposure to high amounts of Al or an increased blood Al concentration may result in reduced renal functionality and can significantly contribute to brain Al accumulation. Al accumulation also occurs physiologically with aging (Mc Dermott et al., 1979).

Experimental findings have demonstrated that Al gets deposited in the brain at a rate of 6µg per year of life (Edwardson et al., 1991). In autopsies performed on healthy people >75 age group (75-102 years), a significantly high brain Al content was estimated when compared to younger people (Shimizu et al., 1994). A proportionately high concentration of Al was observed in the brains of AD patients (Crapper et al., 1976).

High levels of aluminium have been implicated in several neurodegenerative conditions such as Alzheimer’s disease (AD), Parkinson’s disease (PD), pre-senile
dementia, amyotrophic lateral sclerosis, dialysis encephalopathy syndrome and nigrostriatal syndrome (Gupta et al., 2005; Nayak, 2002). Elevation in brain aluminium levels has also been associated with other less prevalent neurological disorders such as the Guamanian Parkinsonian-ALS constellation and Hallervorden-Spatz disease (Eidelberg et al., 1987; Garruto et al., 1989).

In comparison to control mice group, the values of aluminium concentration in melatonin treated were lower and resulted in statistically significant decrease over the control group after 42 day exposure. This may be attributed to the binding property of melatonin to Al and formation of metal complexes (Limson et al., 1998).

However, the group administered with both melatonin and aluminium, Al concentration levels were decreased. This may be due to melatonin ability to neutralize the pro-oxidant action of aluminium and its metal chelating ability. Several studies both in vivo and in vitro have emphasized the protective effect of melatonin against metal-induced oxidative damage (Flora et al., 2004; Parmar et al., 2002; Karbownik et al., 2001).

Chwelatiuk et al. (2006) demonstrated that 8-week melatonin co-administration with oral cadmium chloride, displayed significantly reduced cadmium levels in renal, hepatic and intestinal tissues.

Melatonin has been reported to protect against copper-mediated free radical damage in liver homogenates by binding copper ions as well as by protecting against free radical damage by its antioxidant properties (Parmar et al., 2002). It was reported that melatonin protects against methyl mercury-induced death in mice (Kim et al., 2000).
Melatonin appears to exert its protective effects towards carcinogenesis, neurodegeneration and aging (Melchiorri et al., 1995). A comparatively lower level of melatonin was observed in cerebrospinal fluid of Alzheimer’s patients as compared with the age matched healthy individuals (Lima et al., 2003).

In the present investigation the elevated levels of aluminium content (Table-2.1 and Fig. 2.1) has been observed in different brain regions of albino mice exposed to sub-chronic exposure of aluminium acetate and high concentration of Al was observed in hippocampus region. The elevation in Al content is significantly decreased on supplementation with melatonin in different brain regions. Treatment with melatonin caused the decrement in accumulation of aluminium in different brain regions. During the melatonin treatment the more inhibition of Al content was observed in cerebellum region when compared to other regions i.e., cerebral cortex, hippocampus and medulla oblongata of albino mice.

The results and literature cited above clearly indicated the potential effect of melatonin in reducing aluminium accumulation and consequently its prime role in preventing Al-induced injury in different brain regions of albino mice.