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Original Research Article

Aluminum Chloride Induced Inflammatory process in Rat's Brain

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Abstract

Neurotoxicity is a form of toxicity in which a biological, chemical, or physical agent produces an adverse effect on the structure or function of the central and/or peripheral nervous system. This study was conducted to evaluate the neurotoxic effect of aluminium chloride induced neuroyoxicity in rats. Fourty rats used in this study were divided into two groups: control group, rats were received normal laboratory diet all over the period of the experiment for 8 weeks and aluminium chloride protective group received (i.p) injection of AlCl3 daily at dose (300mg/kg). The results revealed that injection of AlCl3 effected on inflamatory markers where, levels of interleukin (il-2), interleukin-6 (il-6) Tumer Necrosis Factor (TNF α) were significantly increased.

Key words: Aluminum chloride, Interleukin, Nervous system, Neurotoxicity, Inflammation, Rat.

INTRODUCTION

Neurotoxicity refers to the direct or indirect effect of chemicals that disrupt the nervous system of humans or animals. Numerous chemicals can produce neurotoxic diseases in humans, and many more are used as experimental tools to disturb or damage the nervous system of animals. Some act directly on neural cells, others interfere with metabolic processes on which the nervous system is especially dependent. Some disrupt neural function, others induce maldevelopment or damage to the adult nervous system. Perturbations may appear and disappear rapidly, evolve slowly over days or weeks and regress over months or years, or cause permanent deficits. Neurotoxicity is usually self-limiting after exposure ceases and rarely progressive in the absence of continued exposure, although there may be a significant delay between exposure and manifestation of neurotoxic effects [1].

Aluminum (Al) is widely distributed in the environment representing the third prevalent element in the earth's crust [2]. The massive daily life use of Al permits easy exposure to human beings from compounds used in utensils, food additives, water purifiers and pharmaceuticals [3]. In addition, the contamination of the environment with compounds containing aluminum such as particulate matter resulting from cement factories expose the population residing near them to occupational airborne Al particulates [4]. Moreover, exploitation of bauxite mines and acid rain can cause the flux of large amounts of Al salts from insoluble minerals, increasing the risk of human contact with Al. Therefore, further research on the mechanism of Al-induced neurotoxicity is necessary to avoid the hazardous effects of Al [5].

Aluminum is categorized as a neurotoxin which has hazardous effects on the development of the brain, prenatally or postnatally, in humans and experimental animals [6]. It has been reported that the excessive Al intake for long time causes neuroinflammation and deficits in cognitive functions. Neuroinflammation alters dendritic spines density, which, in turn, influences cognitive function [7]. Aluminum can cross the blood brain barrier and accumulate in brain tissues [8] with the highest concentrations in the hippocampus [9].

MATERIAL AND METHODS

Chemicals

Aluminium Chloride was purchased from Sigma–Aldrich, St. Louis, MO, USA.

Animals

All experiments were approved by the Ethical Committee of Faculty of Veterinary Medicine, Benha University. Fourty male Wistar albino rat (150 ± 20g) were supplied by the animal house of Faculty of

Veterinary Medicine, Benha University, Egypt. They were acclimatized in our animal facility for one week under controlled environmental conditions before the experiment. Fresh daily supplies of food and tape water were served ad libitum.

Experimental protocol

Rats were randomly divided into two groups (20 each) and treated for 8 consecutive weeks. Control group: normal rats received saline i.p once daily and considered as a control normal group. AlCl3 group: rats received AlCl3 (300 mg/kg, i.p.) once daily for induction Neurotoxicity [10].

Sampling

Blood samples and brain tissue specimens were collected after overnight fasting from all animal groups twice along the duration of experiment after (4 and 8 weeks).

Blood samples

Rats were fasted overnight then, blood samples collected from retro-orbital venous plexus of eyes in clean dry tubes and incubated for 30 min at room temperature to allow clotting for serum separation then centrifuged at 3000 rpm for 15 min, the clean clear serum aspirated by automatic micropipettes, received in dry sterile eppendorf tubes and kept in deep freezer (-20 °C) until used for biochemical analysis.

Tissue samples

After blood samples collected 10 rats from each group were sacrificed by decapitation, the brain was rapidly excised and clean by rinsing with ice-cold isotonic saline to remove any blood cells and clots, then put it between 2 filter papers and quickly stored in a deep freezer at temperature (-20°C) for biochemical analysis.

Preparation of brain homogenate

After two freeze-thaw cycles were performed to break the cell membranes the homogenates were centrifuged for 5 minutes at 5000r.p.m to separate the supernatant. The supernatant was used for determination of TNF α as an inflammatory marker.

STATISTICAL ANALYSIS

First, all data were tested for normality and homogeneity. Then, one way analysis of variance used to determine the statistical significance of differences among groups followed by Duncan's test as post hoc for making a multiple comparisons using the Statistical Package for Social science Software (Version 25, SPSS Inc., Chicago, IL, USA). The values were expressed as the mean ± standard error of the mean. A significant difference was used at the 0.05 probability level.

RESULTS

The obtained data demonstrated in figure (1) revealed that, administration of AlCl3 to normal rats exhibited a significant increase in serum IL-2, IL-6, TNF-α and brain TNF-α compared with control group.

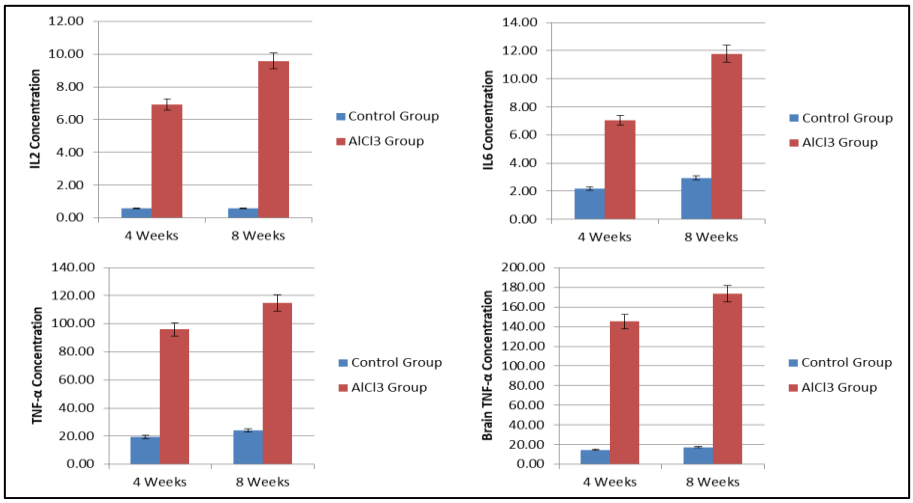

Fig-1: Effect of $AlCl_3$ on inflammatory markers

DISCUSSION

The obtained data demonstrated in figure (1) revealed that, administration of AlCl3 to normal rats exhibited a significant increase in (IL-2), (IL-6) and Tumer Necrosis Factor (TNF α) concentration compared with control group. These results were nearly similar to the reported study of [11] who reported that, a significant increase in the level of cortical and hippocampal TNF-α in AlCl3-treated rat as compared with control group.

Our results demonstrates that AlCl3- induced neurotoxicity is due to accumulation of abnormal protein aggregates, like Ab-42 and free radicals (NO, ROS and RNS), that trigger cellular stress and neuroinflammation by activation of the brain's innate

immune system involving microglia and astrocyte [12, 13, 14] reported that AlCl3 administration enhanced the expressions of pro-inflammatory cytokines such as IL-2 (numerous effects on hippocampal neurons, where its receptors are enriched, thus improving cognitive performances), IL-6 (mediator of the inflammatory and immune responses), TNF-α (trigger for other cytokines). Likewise [15] reported that a dose of (AlCl3) added to the drinking water at a concentration of 53.5 mg/ l showed a Significant elevations in the serum inflammatory markers interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α). In addition to [16], have found a significant increase of pro inflammatory cytokines, IL-6 and TNF-α in treated AlCl3 rats. it has been suggested that accumulation of Al accompanied by the release of cytochrome c from mitochondria, which eventually causes an increase in the production of free radicals triggering oxidative stress by increasing oxidative damage to biomolecules and an increase in the production of proinflammatory cytokines [17]. Further, it results in the increase in the gene expression of TNF-α and the increased TNF-α level plays a crucial role in neuro inflammation-mediated neuro degeneration associated with aluminum neurotoxicity [18]. Also [19] demonstrated that rats exposure to AlCL3 increased pro inflammatory cytokines (IL6 and TNF-α) in hippocampus and frontal cortex with obvious effect in hippocampus.

S.Y. Qusti, M. Balgoon, E.S. Alzahrani, N. Elsawi, N.A [20] reported that injection of AlCl3 causing An increase in expression of inflammatory cytokines IL-6 and tumor necrosis factor-α (TNF-α) has been detected in rats brain and IL-1-positive microglia present with Aβ peptide -containing plaques, a similar event occurs in activated astrocytes. The role of astrocytes in neuroinflammation has been highlighted in the past years with many observations both in vivo and in vitro depicting the importance of these glial cells in this process Increased levels of INF-γ, IL-1β, IL-6, and TNFα induce astrocytes to adopt a classical activation state (increased activation of NF-κB pathway, production of ROS and NO, and release of IL-1β, IL-6, and TNFα), while increased levels of IL-4 and IL-13 induce an alternative activation (increased secretion of IL-4 and decreased production of ROS and NO); oppositely, high levels of IL-10 and TGF-β induce astrocytic deactivation (reduced immune surveillance and proinflammatory signaling).

Al intoxication leads to marked astrocytes and microglial activation that contribute to the pathogenesis of neuroinflammation and neurodegeneration [21]. Chronic administration of AlCl3 causes a greater inflammatory response over immunoreactivity of astrocytes and microglia associated with cognitive dysfunction and disease [22]. Reactive gliosis and the associated proinflammatory cytokines/ chemokines could be result of inflammation and neuronal injury in the rat brain [23]. Inhibition of pro-inflammatory mediators would be a better approach in regulating the progression of neurodegenerative disorders. The pro-inflammatory cytokines, TNF-α and iNOS, contribute to neuronal damage and death in vivo and in vitro [24]. Activation of iNOS in glial cells is a key step in neuroinflammation and is often related with TNF-α release. A potent proinflammatory cytokine TNF-α is synthesized by microglia, astrocytes and neurons [25]. TNF-α together with other transcription factors (NF-κB, nuclear factor kappa B) involved in cell responses including inflammation, proliferation, cell migration and apoptosis [26].

Our results revealed that, AlCl3 injection induced a marked increase in the concentration of IL-2, IL-6 and TNFα as an inflammatory cytokines. These results were in line with the previous study of [19] who found that AlCl3 significantly induces the expression and production of pro-inflammatory cytokines (TNF-α, IL-6,), and enhances the expression of iNOS most probably by immuno-competent and phagocytic cells in CNS. And the increased TNF-α level plays a crucial role in neuroinflammation-mediated neurodegeneration associated with aluminum neurotoxicity.

CONCLUSION

The findings of this study indicate that AlCl3 one of the causes of neurotoxicity. This neurotoxicity effect of AlCl3 may be attributed to tumor markers.

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