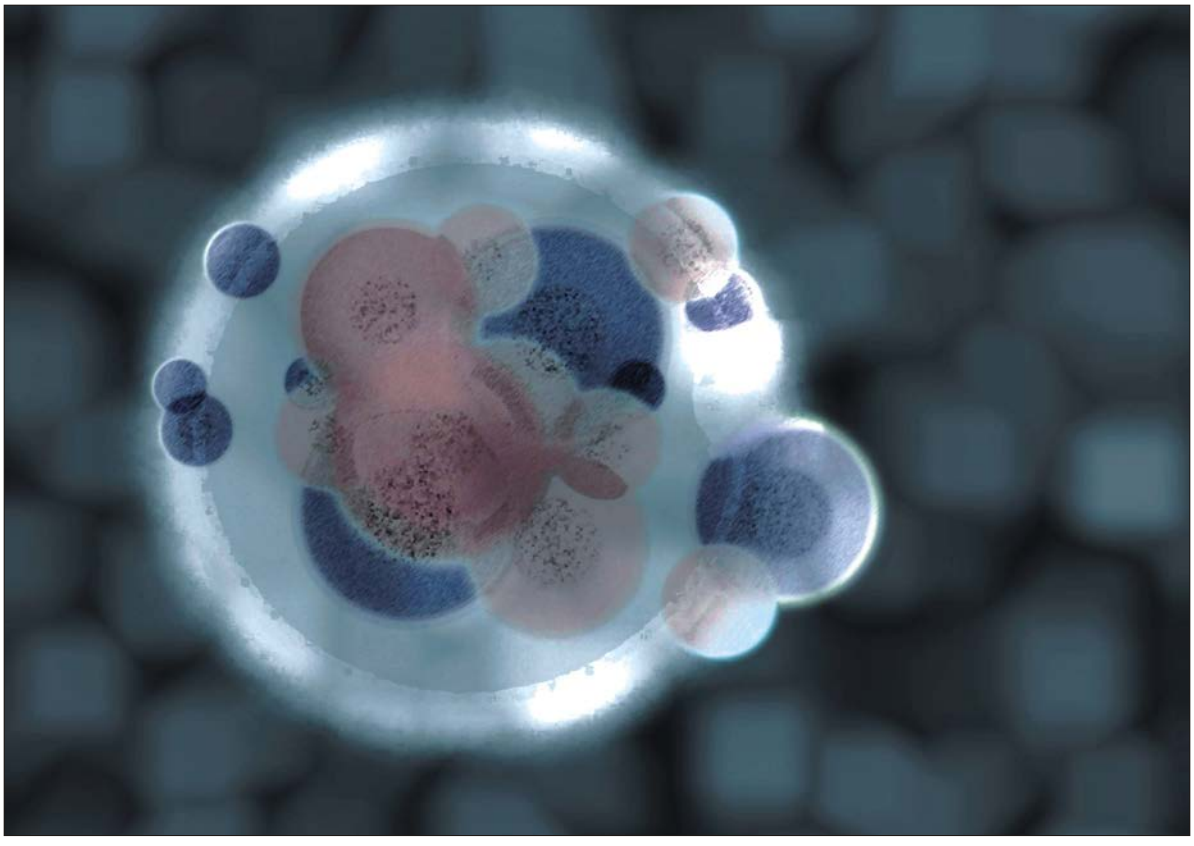

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Effect of Oral Aluminum Chloride Administration During Lactation on Short and Long-Term Memory of Their Offspring

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Abstract: To study the relationship between aluminum chloride ($AlCl_3$) and memory of their offspring male. Five groups of adult Wistar rats (200±30) were taken for this experiment. Female rats were concurrently exposed (0, 200, 400, 600 and 800 mg/kg/day) of aluminum administered as $AlCl_3$ in drinking water for two weeks. Forty-five after birth, a shuttle box was used to test memory. This experiment showed that maternal dietary exposure $AlCl_3$ (200, 400 and 600 mg/kg/day) doses after two weeks during lactation, there were no different on the working memory of their offspring for any of groups. But rat which received $AlCl_3$ 800 mg/kg/day during lactation, has shown significant impairment in working memory of their offspring ($p<0.001$) ($p<0.05$). This study has demonstrated that (200, 400 and 600 mg/kg/day) $AlCl_3$ consumption for two weeks during lactation had no effect. But consumption of $AlCl_3$ 800 mg/kg/day during lactation, can impairment in (short-term and long-term) memory of their offspring.

Key words: Aluminum, lactation, memory, maternal, drinking water, offspring

INTRODUCTION

Many investigators have evaluated the association between oral aluminum exposure and brain development in early life, they showed that aluminum is highly toxic to the growth and development of fetuses and suckling in humans and experimental animals (Bishop *et al*., 1997; Yumoto *et al*., 2000; Sedman *et al*., 1984). It enters humans via water, food, air and drugs (especially antacids) and Aluminum compound added to many commercially-prepared products destined for ingestion (Graves *et al*., 1990). Also is present in all body tissues and organs, including brain (Walton, 2007). Animal studies have documented Central Nervous System (CNS) impairments following aluminum exposure, including neuropathological, neurochemical, neurophysiological and neurobehavioral changes. Among then, a series of studies have been conducted to clarify the deficits of learning and behavioral functions since 1970s (Wang *et al*., 2002). The pathologic features that these neurodegenerative disease share include abnormal phosphorylation of neuronal cytoskeletal proteins and the abnormal deposition of these proteins in neuron (Kawahara, 2005; Liu *et al*., 2005). High concentration of Al reported in plasma and tissue samples of dialyzed and nondialyzed patients with chronic renal failure (Alfrey, 1985; Kaehny *et al*., 1997). Normally, mammals maintain very low Al concentrations in their tissues because of a combination of low intestinal uptake and rapid clearance (Domingo *et al*., 2001).

Studies with pregnant and lactating women may be transferred to fetuses and sucklings; especially its incorporation into their brain (Yumoto *et al*., 1995, 1998). In addition, many others has reported cases of encephalopathy or impaired neurologic development caused by Al intake infants. Also, studies have suggested that exposure to neurotoxic substances in early life causes Alzheimer's disease (AD) in old age has been proposed by Yumoto *et al*. (2000) and Rondeau *et al*. (2000). Al bound to nuclear DNA phosphate and bases, increasing histone- DNA binding, altering sister chromatid exchange and decreasing cell division. The accumulation of Al in DNA may later protein-DNA interactions (Crapper McLachlan *et al*., 1990).

The others attribute the large variability in uptake into brain to individual differences in Al metabolism including gasteroinduct tract absorption, timing of peak plasma concentration of Al, variations in Al-ligand binding, Al excretion values, blood-brain barrier to Al (Walton *et al*., 1995). On the other hand, studies have showed evidence on the similarities and dissimilarities, between Al-induced neurofibrillary degeneration and

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paired helical filaments from AD, the accumulation Al in neurofibrillary tangle and senile plaques from AD, the neuropathological dissociation between AD and dialysis associated encephalopathy (Miu and Benga, 2006).

Because Aluminum is neurotoxic in humans exposed parenterally, via the oral rout in those suffering renal disease and potentially in neonates receiving formulas with excess Al. The aim of this study was to investigate the effects of different doses of Aluminum supplementation during lactation on memory of their offspring.

MATERIALS AND METHODS

Animal: Six Pair of adult wistar rats (200±30 g) were chosen for this experiment. They were maintained in a 12 h light: dark cycle and temperature-controlled (22-25°C) animal room (Wang *et al*., 2001a). All animals were provided by Ahvaz Medical University's animal house in Iran. This study was performed from April to December 2007. Female rat were placed in cages for time mating with males. Then lactating rats were separated from male rats as they were divided into five batches. One batch was the control batch with free access to food and water and the other five groups were drunken Aluminum chloride in different doses (200, 400, 600 and 800 mg/kg/day) in their drinking water for two weeks of lactation. Dams and their litters then were housed in stainless cages. All litters were weaned for 37 days, fed and lib and drank tap water until they became 45 days old.

Apparatus: A shuttle box, as The apparatus used for passive avoidance response training of their offspring that consisted of two adjacent Plexiglas compartments of identical dimensions 27×14.5×14 cm two compartments were separated by a guillotine door in the middle part of this apparatus. According to compartments, one is illuminated and the other is dark. A sliding door separated the two compartments and could be lowered from a 2.5 cm hurdle. The floor consisted of 6 mm diameter stainless-steel rods spaced 1.7 cm between centers. The rods were connected to shock generator which could deliver to the compartment as a scrambled foot shock. A flashing light (7.5 W) was fixed to the outside wall of the white chamber (Moazedi *et al*., 2007).

Procedure: On the first day Acquisition rats had free access to either the light or dark compartment of the box. On the second day (Training) rat was placed in the illuminated compartment and after 30 sec the guillotine door raised. For entering the dark compartment the door was closed and a 1.5 mA constant current shock was applied for 2 sec, then after 20 sec the rat was removed from the dark compartment and placed in to the home cage. For testing short and long-term memory, after a 48 h passive avoidance response training, the rat was placed in illuminated chamber and 30 sec later the guillotine door was raised and both the latency of entering the dark compartment (step-through latency) and the time spent there during 5 min was recorded (Takeda *et al*., 2005; Arlene *et al*., 1997). We also did this procedure 30 days after passive avoidance response training,

Data were analyzed by one way analysis of variance (ANOVA) for testing long-term memory which followed by post hoc test. The level of significance was set at $p<0.05$.

RESULTS

The received data of step-through latencies shows that there were no significant different between rats control batch and rats that their mothers received $AlCl_3$ (200, 400, 600 and 800 mg/kg/day) at the stage of lactation 48 h after training. But in this step, there was significant difference between rats that their mothers received $AlCl_3$ (800 mg/kg/day) at the stage of lactation and control group ($p<0.001$) (Fig. 1).

Thirty days after training there was not any significant difference between control batch and groups that their mothers received Aluminum chloride in different doses at the stage of lactation, but in this step, there was

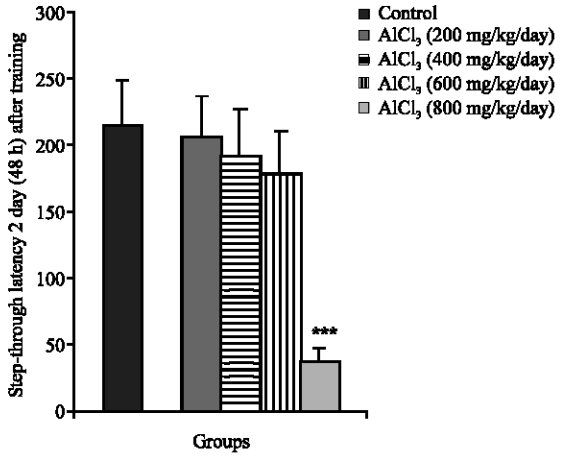

Fig. 1: Effect of aluminum chloride on step-through latency 2 day (48 h) after training. ***$p<0.001$, $n = 8$

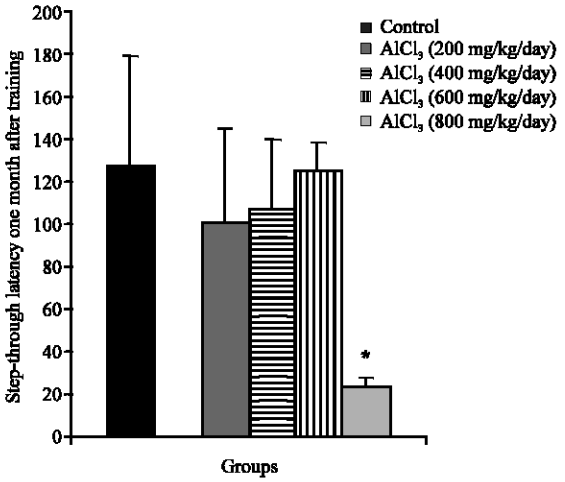

Fig. 2: Effect of aluminum chloride on step-through latency one month after training. *p<0.05, n = 8

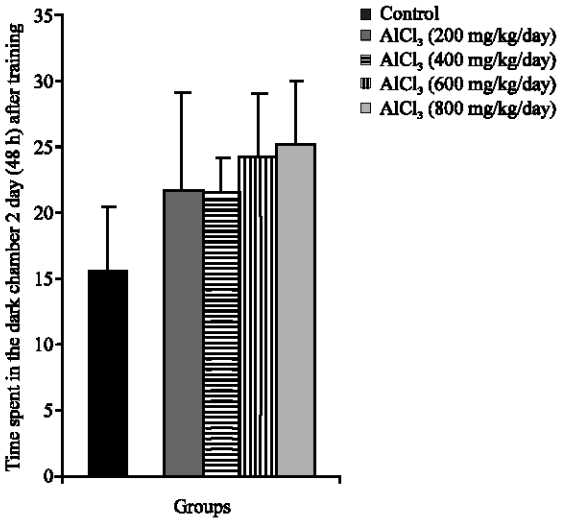

Fig. 3: Effect of aluminum chloride on time spent in the dark chamber 2 day (48 h) after training n = 8

significant difference between rats that their mothers received $AlCl_3$ (800 mg/kg/day) at the stage of lactation and control group ($p<0.05$) (Fig. 2).

On the other hand, statically analysis of data in the time spent at the dark chamber, 48 shows that there were no significant different between rats control group and rats that their mothers received $AlCl_3$ (200, 400, 600 and 800 mg/kg/day) at the stage of lactation 48 h after training (Fig. 3).

Thirty days after training there was not any significant difference between control batch and any of groups that their mothers received zinc chloride in different doses at the stage of lactation (Fig. 4).

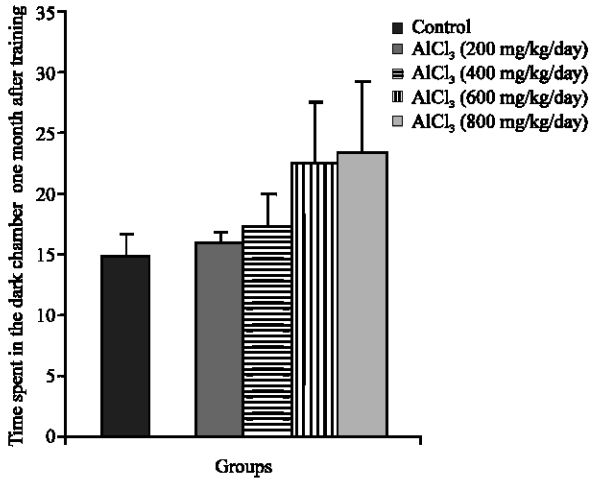

Fig. 4: Effect of aluminum chloride on time spent in the dark chamber one month after training n =8

DISCUSSION

Aluminum is environmentally abundant, but not an essential element and has no known biological function (Jansson, 2001). Most behavioral studies have shown chronic Aluminum exposure will cause behavioral deficits in animals. In the present study, our result shows that, $AlCl_3$ consumption (200, 400 and 600 mg/kg/day) for two week at the stage of lactation, could not significant effect on short-term and long-term memory of their offspring. This result is similar to the result of some other investigators. For instance, (Golub *et al*., 1995) development exposure (from parturition to weaning) to 500 and 1000 μg aluminum/g diets had distinctive long-term effects on behavioral measures that were not dose dependent and were not further intensified by continuing exposure as adults also, indicated that, a lack of remarkable Al transfer with lactation would not necessarily indicate that elevated Al in milk doses not cause adverse effects on the offspring (Domingo *et al*., 2000). In another study, has reported that prenatal Aluminum exposure had no effect on the acquisition of a conditioned taste aversion, but a passive avoidance task learning ability of pups of dams given the highest dose of Aluminum was impaired (Gonada and Lehotzky, 1996; Kim, 2003). On the other hand, results of the previously studied did not show a notable influence of maternal restraint on the Al induced postnatal development and behavioral effects in the offspring of prenatally Al-exposed rats (Colomina *et al*., 2005). These result confirmed our results in this experiment. However (800 mg/kg/day) for two week at the stage of lactation, could be significantly ($p<0.001$) impairment working

memory in their offspring. This study, as well as other investigations conducted on rats, showed that nursing pups of mouse dame fed excess Al in their diet exhibit poor retention of iron and manganese from a milk meal (Gonda and Domingo, 1996). In addition, maternal dietary exposure to excess aluminum during gestation and lactation which did not produce maternal toxicity would be capable of causing permanent neurobehavioral deficits in weanling mice and rats (Golub *et al*., 1996). Also, showed that oral Al administration to rats during pregnancy and lactation produced delay in the development of the central nervous system of their pups (Poulos *et al*., 1996). On the other hand Walton (2007) and Gong *et al*. (1995) shown that aluminum can account for the earliest known changes that occur in AD; aluminum causes oxidative damage in brain regions vulnerable to AD change in humans; Aluminum inhibits PP24 activity *in vivo* and Aluminum induces the formation of hyperphosphorylated tau. These are the same changes that proceed and lea to plaque and tangle formation in the human brain. This result confirmed our result in this experiment. Furthermore, other scientist reported that Al administered to pregnant rats and/or lactating rats is transferred to their offspring through tansplacental passage and/or maternal milk. Al incorporated into fetuses and suckling rats may cause growth retardation in various organs including the brain (Bishop *et al*., 1997). The investigations indicate Al- induced impairment of N-methyl-D-aspartate (NMDA) receptor associated signal transduction pathways. The effect was selective for proteins of the glutamate-nitric oxide-cGMP pathway, suggesting a possible mechamism for the neurotoxic effects of Al (Liansola *et al*., 1999). Also some scientists have shown that long-term potentiation (LTP) and long-term depression (LTD) two forms of synaptic plasticity are believed to underlie learning and memory (Barnes, 1995). In area CA_1 of hippocampus, induction of LTP and LTD requires NMDA receptor activation a postsynaptic increase in calcium and metabotropic glutamate receptors (mGLUR) (Shi *et al*., 2005; Trommer *et al*., 1996). Further, aluminum exposure also decreases the (adenine tree phosphate enzyme) ATPase activity which in turn could affect the glutathione synthesis. So, the lesion of Aluminum on learning memory relates to the change of intracellular calcihemeotasis, the decrease of protein kinase c (pkc) activity and some neurotransmitter, which can change the memory, such as, aminoglutaric acid, gamma amino butyric acid, acetylcholine and deficits in both LTP and LTD rat dentate gyrus area *in vivo* (Wang *et al*., 2001; Chen *et al*., 2002; Platt *et al*., 1995). The authors suggest that genetic differences in the permeability of the blood brain barrier to Al may be an important variable in Al toxicity (Walton *et al*., 1995). On the other hand following experimental aluminum exposure, significant increase in lipid peroxidation occurs in brain tissue of rat pups even as young as 39 days of age (Nehru and Anand, 2005). Some scientists in their investigations have shown that Aluminum negative effect in long-term memory. High serum levels of Aluminum in elderly humans are associated with impaired long-term memory and increased sensitivity to flicke (Bowdler *et al*., 2002). That confirms our result in this research with 800 mg/kg/day Aluminum chloride consumption ($p<0.001$). It seems high concentration of Aluminum chloride in lactation period could impairment memory of their offspring.

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REFERENCES

Alfrey, A.C., 1985. Gastrointestinal absorption of aluminum. Clin Nephrol., 24: s53-s57.

Arlene, C., W.A. Rodringuez and T.P. Wright, 1997. Time-dependent effects of fruetose on the modulation of reactivated memory. Prog. Neuro Psymemory, 21: 649-658.

Barnes, C., 1995. Involvement of LTP in memory. Neuro, 15: 751-754.

Bishop, N.J., R. Morley, B. Chir, J.P. Day, A. Lucas and N. Engl, 1997. Aluminum neurotoxicity in preterm infants receiving intravenous feeding solution. Medicine, 336: 1557-1562.

Bowdler, N.C., D.S. Bealey and E. Cristina Fritze, A.M. Goulette, J.D. Hatton, J. Hession, Ol. Ostman, D.J. Rugg and C.J. Schmitdel, 2002. Behavioral effects of aluminum ingestion on animal and human subjects. Pharmacol. Biochem. Behav., 10: 502-552.

Chen, J.T., M. Wang, D.Y. Ruan and J.Q. She, 2002. Early chronic aluminum exposure impairs long-term potentiation and depression to the rat gyrus *in vivo*. Neuroscience, 113: 411-419.

Colomina, M.T., J. Roig, M. Torrente, P. Vicens and J. Doming, 2005. Concurrent exposure to aluminum and stress during pregnancy in rat: Effects on postnatal development and behavior of the offspring. Neurotoxico Teratol., 27: 565-574.

Crapper McLachlan, D.R., W.J. Lukiw and T.P.A. Kruck., 1990. Aluminum, altered transcription and the pathogenesis of Alzheimers disease. Environ. Geochem. Health, 12: 103-114.

Domingo, J., M. Gomez and T. Colomina, 2000. Risks of aluminum exposure during pregnancy. Science, 1: 479-487.

Domingo, J.L., 2001. Aluminum: Toxicology. In: Encyclopedia of Food Science, Food Technology and Nutrition, Macrae, R., R. Robinson and M. Sadler (Eds.). Academic Press, London.

Golub, M.S., B. Han, C.L. Keen, M.E. Gershwin and R.P. Tarara, 1995. Behavioral performance of Swiss Webster mice exposed to excess dietary aluminum during development or during development and as adults. Toxicol. Applied Pharmacol., 133: 64-72.

Golub, M.S. and J.L. Domingo, 1996. What we know and what we need to know about developmental aluminum toxicity. Toxicol. Environ. Health, 48: 585-597.

Gonada, Z. and K. Lehotzky, 1996. Effect of prenatal aluminum lactate exposure on conditioned taste aversion and passive avoidance task in the rat. Applied Toxicol., 16: 529-532.

Gonda, Z., K. Lehotzky and A. Miklosi, 1996. Neurotoxicity induced by prenatal aluminum exposure in rat. Neurotoxicology, 17: 459-470.

Gong, C.X., S. Shaikh, J.Z. Wang, T. Zaidi, I. Grundke-Iqbal and K. Iqbal, 1995. Protein phosphatase activity towards abnormally phosphorylated tau: Decrease in Alzheimer disease brain. Neurochemistry, 65: 732-738.

Graves, A.B., E. White, T.D. Koepsell, B.V. Reifler, G. van Belle and E.B. Larson, 1990. The association between aluminum-containing products and Alzheimer's disease. J. Clin. Epidemiol 43: 32-44.

Jansson, E T., 2001. Aluminum exposure and Alzheimer's disease. Alzheimer's Dis., 3: 541-549.

Kaehny, W.D., A.P. Hegg and A.C. Alfrey, 1997. Gastrointestinal absorption of aluminum from aluminum-containing antacids. Medicine, 296: 1389-1390.

Kawahara, M., 2005. Effect of aluminum on the nervous system and its possible link with neurodegenerative diseases. Alzheimer's Dis., 8: 71-82.

Kim, K., 2003. Perinatal exposure to aluminum alters neuronal nitric oxide synthase expression in the frontal cortex of rat offspring. Brain Res. Bull., 61: 437-441.

Liansola, M., M. Dolores Minana, C. Montoliu, R. Saez, R. Corbalan, L. Manzo and V. Flipo, 1999. Prenatal exposure to aluminum reduces expression of neuronal nitric oxide synthase and of soluble guanylate cyclase and impairs glutamatergic neurotransmission in rat cerebellum. Neurochemistry, 73: 712-718.

Liu, F., I. Grundke Iqbal, K. Iqbal and C.X. Gong Eur, 2005. Contribution of protein phosphatases PP1, PP2A, PP2B and PP5 to the regulation of tau phosphorylation. Neuroscience, 22: 1942-1950.

Miu, A.C. and O. Benga, 2006. Aluminum and Alzheimer's disease. Alzheimer Dis., 10: 165-175.

Moazedi, A.A., Z. Ghotboddin and G.H. Parham, 2007. The effect of zinc supplementation of pregnant rats on short-term and long-term memory of their offspring. Med Sci., 23: 1-5.

Nehru, J. and J. Anand, 2005. Oxidative damage folloing chronic aluminum exposure in adult and pup rat brains. Med. Biol., 19: 203-208.

Platt, B., D.O. Carpenter, D. Busselberg, K.G. Reymann and G. Riedel, 1995. Aluminum impairs hippocampal long-term potentiation in rat *in vitro* and *in vivo*. Exp. Neurol., 134: 73-86.

Poulos, B.K., M. Perazzolo, V.M. Lee, R. Rudelli, H.M. Wisniewski and D. Soifer, 1996. Oral aluminum administration during pregnancy and lactation produces gastric and renallesion in rat mother and delay in CNS development of their pups. Mol. Chem. Neuropathol., 29: 15-26.

Rondeau, V., D. Commenges, H. Jacqmin-Gadda and J.F. Dartigues, 2000. Relation between aluminum concentrations in drinking water and Alzheimer's disease: An 8-year follow-up study. Am. J. Epidemiol., 152: 59-66.

Sedman, A.B., G.N. Wilkening, B.A. Warady, G.M. Lum and A.C. Alfrey, 1984. Encephalopathy in childhood secondary to aluminum toxicity. Pediatrics, 105: 836-838.

Shi, L.S., Y.M.A. Guang, L.H. Bachlor, Z.Y. Bachelor, H.M. Dong and X.H. Xu, 2005. Effect of naloxane on aluminum-induced learning and memory impairment in rats. Neurology, 53: 79-82.

Takeda, A., H. Tamano and M. Tochigi, 2005. Zinc homeostasis in the hypocamppus of zinc-deficient young adult rats. Neurochem. Int., 46: 221-225.

Trommer, B.L., Y.B. Liu and J.F. Pasternak, 1996. Long-term depression at the medial perforant path-granule cell synapse in developing rat dentate gyrus. Dev. Brain Res., 96: 97-108.

Walton, J., C. Tumz, D. Fink, G. Jacobsen and D. Wilcox, 1995. Uptake of trace amounts of aluminum into the brain from drinking water. Neurotoxicology, 16: 187-190.

Walton, J.R., 2007. An aluminum-based rat model for Alzheimer's disease exhibits oxidative damage, inhibition of PP2A activity, hyperphosphorylated tau and granulovacuolar degeneration. Inorganic Biochem., 101: 275-284.

Wang, F.D., W. Bain, L.W. Kong, F.J. Zhao, J.S. Guo and N.H. Jing, 2001. Maternal zinc deficiency impairs brain nestin expression in prenatal and postnatal mice. Cell Res., 11: 135-141.

Wang, M., J.T. Chen, D.Y. Ruan and Y.Z. Xu, 2001. Vasopressin reverses aluminum-induced impairment of synaptic plasticity in the rat dentate gyrus *in vivo*. Brain Res., 899: 193-200.

Wang, M., J.T. Chen, D.Y. Ruan and Y.Z. Xu, 2002. The influence of developmental period of aluminum exposure on synaptic plasticity in the adult rat dentate gyrus *in vivo*. Neurosociology, 113: 411-419.

Yumoto, S., S. Kakimi, H. Matsushima, A. Ishikawa and Y. Homma, 1995. Progress in Alzheimers and Parkinson? s Diseases Recent Development. 1st Edn. Plenum, New York, pp: 223.

Yumoto, S., S. Kakimi , H. Matsushima, A. Ishikawa and Y. Homma, 1998. Progress in Alzheimers and Parkinson? s Diseases. 1st Edn. Plenum, New York, pp: 293.

Yumoto, H. Nagai, H. Matsuzaki, T. Kobayashi, W. Tada, Y. Ohki, S. Kakimi and K. Kobayashi, 2000. Transplacental passage of Al from pregnant rats to fetuses and AL transfer through maternal to suckling rats. Nuclei Instrum. Phys., 172: 925-929.