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Neurobehavioral toxic effects of perinatal oral exposure to lithium on the developmental motor reflexes, cognitive dysfunction and brain oxidative stress of mice offspring

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Abstract

In the present study, the perinatal oral exposure of pregnant mice to 15 and 30mg/kg lithium (lithium chloride) in their drinking water resulted in a significant and dose-dependent reduction in postnatal body weight gain, delays in opening of the eyes and appearance in the body hair fuzz, and deficits in the sensory motor reflexes of the mice pups during weaning period (from the day of birth to postnatal day21). At adolescent and adult ages of the male offspring, a significant and dose-dependent deficit was also observed in their learning capability (at PD25), and cognitive behavior (at PD30-36). Furthermore, a significant and dose-dependent disturbance in the levels of neurotransmitters like dopamine (DA) and serotonin (5-HT); non-enzymatic oxidative stress (OS) indices like thiobarbituric acid-reactive substances (TBARS) and total reduced glutathione (GSH); and enzymatic OS indices like glutathione S-transferase (GST), catalase (CAT), and superoxide dismutase (SOD) were observed in the forebrain region of the offspring at post-natal day (PD)7, PD14, PD21, PD30, and PD36. Thus, perinatal lithium exposure can affect the in utero developing fetus, raising the concerns for a potential neurotoxic hazards and a longer lasting cognitive dysfunction. A reduced use of lithium during pregnancy is of crucial importance in preventing lithium -induced neurotoxicity in the offspring.

Keywords: Lithium; Perinatal; Mice offspring; Developmental; Neurobehavior; Oxidative stress

1. Introduction

Lithium salt is commonly used worldwide as an important drug for the treatment of bipolar manic disorders and manic depression (Lenox and Hahn, 2000; Grimes and Jope, 2001; Chuang et al., 2002). Prolonged usage of lithium within therapeutic doses and exposure to its different forms of compounds through various sources like metallurgical processes, pharmaceuticals, air conditioning, dehumidifiers, ceramics and lubricant industries, and from biological and chemical laboratories, induce substantial toxic effects (Zarnescu and Zamfirescu, 2006). Lithium is easily absorbed from gut, gets distributed readily in the extracellular fluid and then accumulates throughout in the body tissues and almost entirely excreted through kidneys (Rosenthal and Goodwin, 2006; Dhawan et al., 1987). Lithium salt is known to affect metabolism, and cause disturbances in neuronal communication and cell proliferation (Phiel and Klein, 2001). Furthermore, lithium is also reported to induce oxidative stress in rat brain (Bhalla et al., 2007).

Long-term developmental effects of lithium exposure have not been studied amply in human populations, although continuous use of lithium throughout the gestation period has been associated with perinatal complications like transient neurodevelopmental deficits, depressed neurological functions in the newborns, teratogenic risk to the developing fetus and toxic effects in the neonatal offspring (Kozma, 2005; Gentile, 2012). On the contrary, it has also been reported that continuous lithium therapy to the mothers during pregnancy does not have any adverse effect on

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neonatal behavioral development of their children (Lugt et al., 2012). However, the possibility of realistic long-term effects on the developing fetal brain due to lithium doses during pregnancy cannot be ruled out completely (Simone et al., 1994; Iqbal et al., 2001; Carlezon and Konradi, 2004). It is well documented that the brain develops mostly during the first trimester of the pregnancy making it highly vulnerable to the cognitive and neurological impact of various drugs used during pregnancy (Tueth et al., 1998). Long term effects of lithium exposure during perinatal period have not been studied in human (Gentile, 2010).

In animals as well, although some long term effects of lithium exposure have been studied in preadolescent developing rat brains reporting for increases in anxiety – like behavior (Youngs et al., 2006) and in adult rats for some oxidative damages in the kidney, liver and brain Toplan et al., 2016), studies in offspring have not been undertaken in details except for the study of Abu-Taweel (2012) that relates with the perinatal exposure effects to lithium on some sensory reflexes, locomotory behavior, and some biochemical enzymes in brain and liver tissues of the mice offspring.

The fact that maternal stress during pregnancy can have serious negative effects on the cognitive dysfunctions of the offspring (Nishio et al., 2001; Sternberg and Ridgway, 2003), the present study was undertaken to explore the effects of perinatal oral lithium-administration to pregnant mice in the offspring at various postnatal developing ages for neurobehavioral, cognitive and biochemical (brain neurotransmitters and oxidative stress indices) effects to assess for a possibility of longer lasting effect of lithium toxicity in the offspring. Data on maternal effects however; has not been included herein and shall form a part in a separate communication.

2. Material and methods

2.1. Animals

Three females to one male Swiss–Webster strain mice (10–12 weeks old) were maintained in each opaque plastic cages measuring 30×12×11 cm, under reversed lighting conditions (with white lights on from 22.30 to 10.30 h local time) and at an ambient temperature (regulated between 18 and 22 °C). On the day one of pregnancy (appearance of vaginal plug was considered as day one of pregnancy), the males were removed from the cages and the females were subjected to experimental treatments. Food (Pilsbury's Diet) and water were available ad libitum, unless otherwise indicated. All study protocol and animal handling procedure were approved by the Research and Ethics Committee of King Saud University, Riyadh, Saudi Arabia and all precautions were taken to minimize animal stress and pain in the animals.

2.2. Lithium treatment and experimental design

The pregnant mice were divided into 3 groups of 10 pregnant mice in each. The first group (Group I) serving as the control group received plain tap water only. Whereas the second and third groups (Group II and III respectively) were treated with 15 and 30 mg/kg body weight per day respectively with lithium in the form of lithium chloride ($LiCl_2$) respectively, dissolved in plain tap water, through oral administration. Our pilot studies have shown that the normal and/or pregnant mice on an average consume 30ml water per day and thus the lithium doses were prepared accordingly. These lithium doses formed the sole drinking fluid source for the experimental group of pregnant mice during the required period of the experiment and represent as Low Lithium and High Lithium doses in all figures and tables of the present study. Fresh lithium doses were replaced in the drinking bottle every day. All pregnant mice were housed individually. Treatment started from day one of pregnancy and was continued until post-natal day 15 (PD 15) and thereafter the mothers were switched to plain tap water. The pups of each experimental group were culled to only eight per dam on the post-natal day 1 (PD 1) after birth and were left with their mothers until PD 22. During this weaning period, three male pups of each litter were color marked from the others, and were subjected to various behavioral tests (described below) under dim lighting (ca 8 lux). In all, 21 pups belonging to seven

litters from each treatment category were considered. All observations were recorded on PD 1 and repeated every other day until PD 21 in the same cohort of three color marked male pups of each litter. These observations were used to measure the early development of sensory motor coordination reflexes together with morphological development in the pups. For statistical analysis, the mean of all three cohorts (color marked pups) per litter was considered as a single score. Thus, seven replicates from each treatment category were considered for the following observations.

2.3. Physical assessment during weaning period

Physical developmental landmarks like body weight, opening of the eyes and appearance of body hair fuzz, were evaluated in the developing offspring starting from day 1 after birth (PD 1) through the entire weaning period until PD 21.

2.3.1. Body weight

Weight is a useful indicator of development. Thus, the pups were weighed every alternate day from PD 1 until PD 21.

2.3.2. Eye opening and hair appearance

The day at which the body hair fuzz appeared, and the eyes opened was also recorded. These two parameters are also useful morphological indicators of development.

2.4. Neuromotor maturation assessment during weaning period

The neuromotor maturation of the developing reflexes in the developing offspring were measured on every alternate day starting from day 1 after birth (PD 1) through the entire weaning period until PD 21.

2.4.1. Righting reflex

The time taken by a pup placed on its back to turn over and place all four paws on the substrate was recorded. An upper limit of 2 min was set for this test.

2.4.2. Cliff avoidance

Pups were placed on the edge of a table top with t the forepaws and face over the edge. The time taken by the pup to back away and turn from the "cliff" was recorded. Again an upper limit of 2 min was chosen. A latency of 2 min was attributed when the animal fell from the "cliff".

2.4.3. Rotating reflex

The surface used to measure the rotating reflex was the same as that used for righting reflex, except that it was inclined at an angle of 30°. The pups were placed on this surface with their heads pointed downward. The time elapsed until the pup rotated its body through180° geonegatively and faced its head upward, was recorded as the rotating time. The upper limit of this test was also set at 2 min.

2.5. Cognitive behavioral assessment during post-weaning period

The following tests were evaluated in the same cohort of male offspring (bearing in mind to include representatives of each litter) in all the behavioral tests.

2.5.1. Active avoidance responses

The active avoidance responses were measured in the animals at PD 25, using an automatic reflex conditioner "shuttle box" (Ugo Basile, Comerio, Varese, Italy). The rectangular shaped shuttle-box was divided into two chambers of equal size by a stainless-steel partition with a gate providing access to the adjacent compartment. Before starting the trial sessions, each animal was allowed to adapt and acquaint itself with the shuttle box for 2 min without any stimulus. A 6 s duration light (21 W) and buzzer (670 Hz and 70 dB) were switched on consecutively and used as a conditioned stimulus (CS).

The CS preceded the onset of the unconditioned stimulus (US) by5 s. The US was an electric scrambler shock (1 mA for 4 s) applied to the grid floor. If the animal avoided the US by running into the other compartment within 5 s after the onset of the CS, the microprocessor recorder unit of the shuttle box recorded an avoidance response and

this was considered as conditioned avoidance response to avoid the electric shock. Each animal was given 50 trials with a fixed inter-trial interval of 15 s. During the 50 trial session of the individual animal, the total number of avoidance was measured. The total time taken until the animal entered the other compartment to avoid the shock treatment (latency of avoidance response or escape latency in seconds) was also measured for each animal and the results were expressed for each group of animals. The spontaneous migration of the mouse to the other compartment between trials was also assessed by measuring the number of crossings between the chambers when no shock was present during UCS and CS (inter-trial crossing). The recorder unit of the automated shuttle box continuously recorded these parameters during the whole experimental period (50 trials) of each animal.

2.5.2. Morris water-maze test

The test has been extensively used to assess cognitive functions in rats (Rutten et al., 2002; Tariq et al., 2008) and mice (Lamberty and Gower, 1991a, 1991b) models. Starting at the age of PD 30, the mice offspring were tested for visual–

spatial memory using a water-maze (Morris 1984). The water-maze consisted of a galvanized white circular water tank (90 cm diameter, 50 cm height) filled with clear tap water (22±1 °C) to a depth of 15 cm. A 6×6 cm size, stainless steel, adjustable, white, escape platform was placed 1 cm below the water level and 13 cm from the rim. The water was made opaque by addition of 1 l of milk, which prevented visualization of the platform. Four points on the rim of the tank were designated north (N), south (S), east (E) and west (W), thus dividing the pool into four quadrants (NW, NE, SE and SW). On the first day, each offspring (P 30) was allowed to swim freely in the pool for 60 s without the platform present in the pool. This free swim enabled the mice to become habituated to the training environment. On days 2–5, offspring (P 31 to P 35, respectively) were trained for 24 trials (six trials a day, with an inter-trial interval of 30 s) to locate and escape onto the submerged platform. At the start of each trial, the mouse was held facing the perimeter of the water tank and dropped into the pool to ensure immersion. The latency from immersion into the pool to escape onto the hidden platform (maximum duration of trial 120 s) was recorded. If the mouse did not find the platform in 120 s, it was manually guided with the help of a glass rod to mount on the platform and a score of 120 s was recorded for each of such experimenter-terminated trials. The number of such unsuccessful trials was counted and expressed as a percentage of failures on each testing day. On mounting the platform, each mouse was given a 30 s inter-trial interval for rest and for learning and memorizing the spatial cues to reach the platform for escape. To minimize handling, at the end of the trials, the animals were allowed to climb onto a wire mesh grid and transferred to their cage without further handling. On day 6, P 36 mice were subjected to a 120 s probe trial in which the platform was removed from the pool. The time spent in each quadrant (within 120 s probe test time) was recorded on an electronic time recorder. In this part of probe trials in water-maze test, normal animals typically spend more time in the quadrant where the platform had been previously located than in the other quadrants. The testing procedures used during the four days of locating the hidden platform provide a measure of hippocampal-dependent spatial reference memory, while the probe trial is a measure of the strength of spatial learning, the closest parallel to episodic memory in humans (Jeltsch et al., 2001; Spiers et al., 2001).

2.5.3. Biochemical studies

For biochemical studies, a sub-set of developing offspring (n=8/group) were sacrificed at different ages (PD 7, 14, 21, 30 and 36) and the level of some neurotransmitters and some enzymatic and non-enzymatic oxidative stress indices were estimated in their fore-brain. The animals were killed by decapitation and the brains were dissected on ice. The fore-brain was isolated (including the cerebral areas with hippocampus and striatum) and frozen in liquid nitrogen and stored at −70 °C for determination of neurotransmitters.

2.5.4. Determination of monoamines

The monoamine neurotransmitters dopamine (DA) and serotonin or 5-hydroxytryptamine(5-HT) were estimated using the modified method (Patrick et al., 1991). A 10% homogenate of the fore-brain was prepared by homogenizing the tissues for 10 s in 0.1 M $HClO_4$ containing 0.05% EDTA, centrifuged at 17,000 rpm at 4 °C for 5 min. The supernatants were filtered using 0.45 µm pore filters and analyzed by high performance liquid chromatography (HPLC). The mobile phase consisted of 32 mM citric acid monohydrate, 12.5 mM disodium hydrogen orthophosphate, 7% methanol, 1 mM octane sulfonic acid and0.05 mM EDTA. The mobile phase was filtered through 0.22 µm filter and degassed under vacuum before use. µBond pak C18 column was used at a flow rate of 1.2 ml/min and the injection volume of the samplewas 20 µl. The levels of DA and 5-HT were calculated using a calibration curve and results were expressed as ng/mg tissue weight.

2.5.5. Determination of non-enzymatic oxidative stress indices

Lipid Peroxides

Lipid peroxides (LP) in the fore brain tissue were determined spectrophotometrically as thiobarbituric acid-reactive substances (TBARS) according to the method of Ohkawa et al. (1979). Tissue lipid peroxide levels were quantified using extinction coefficient of 1.56×10^5 m^{-1} cm^{-1} and expressed as nano moles of TBARS formed per g tissue weight. The results are expressed as nmol/g wet weight.

Glutathione

Reduced glutathione (GSH) level was measured enzymatically in the forebrain tissues by a slightly modified method (Mangino et al., 1991). The slope of the change in absorbance was used to quantitate total GSH by comparing the slope of the samples with a standard curve prepared with pure glutathione (Sigma). The specific activity is expressed into umol/g tissue weight.

2.5.6. Determination of enzymatic oxidative stress indices

Glutathione-S-Transferase. Glutathione S-transferase (GST) was estimated by the method of Habig et al. (1974) using 1-chloro-2,4-dinitrochlorobenzene (CDNB) as substrate at 340 nm. The GST activity is expressed as U/g tissue weight.

Catalase

Catalase (CAT) activity was measured by the method of Aebi (1972) by tracking the decomposition of hydrogen peroxide by measuring decrease in extinction of H2O2 at 240 nm. The activity of CAT is expressed as rate constant of first order reaction K per gram tissue weight.

Superoxide Dismutase

Superoxide dismutase (SOD) activity was estimated by the method of Misra and Fridovich (1972). Activity is expressed as the amount of enzyme that inhibits the oxidation of epinephrine by 50% which is equal to U per gram tissue weight.

2.6. Statistical analysis

All data were analyzed by one-way analysis of variance (ANOVA), between the experimental groups followed by Student-Newman-Keuls multiple comparison test. The levels of significance were defined at $P \leq .05$, $P \leq .01$, and $P \leq .001$.

3. Results

3.1. Physical assessment during weaning period

Physical developmental landmarks were evaluated in the developing offspring starting from the day 1 after birth (PD1) through entire weaning period unto PD21. The lithium exposed offspring at both doses, showed a significant decline ($p<0.05$) in their body weight gain as compared to the controls, from PD2 onwards up to the weaning period (PD21). The lithium exposed offspring remained lagging behind the controls in body weight very significantly ($p<0.001$) in a dose-dependent manner (Fig. 1).

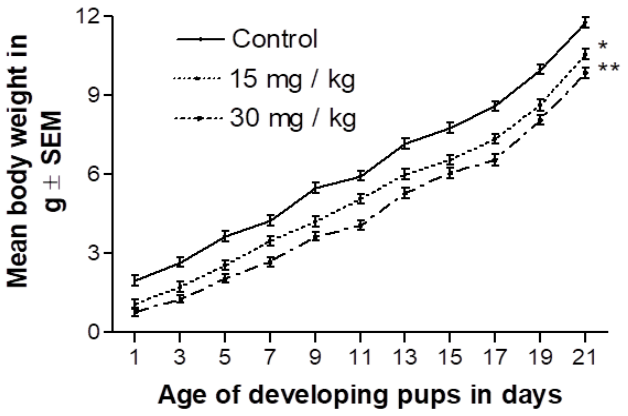

Figure 1 Effect of perinatal lithium doses (15 and 30 mg/kg body weight) exposure on the dose-dependent body weight gain of mouse pups during the weaning (lactation) period. *, ** and *** represent statistically significant (*P<0.05, P<0.01 and P<0.001respectively)* from the control group; see text.

Other morphological developments such as the opening of the eyes and appearance of body hair fuzz were also significantly ($p<0.01$) delayed in the lithium exposed offspring in a dose-dependent manner (Fig. 2).

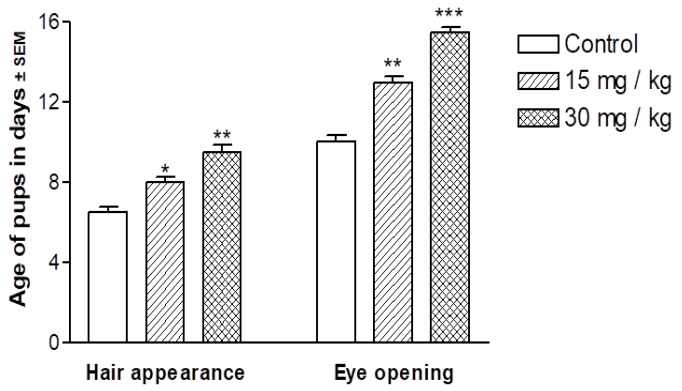

Figure 2 Effect of perinatal lithium doses (15 and 30 mg/kg body weight) exposure on the dose-dependent body hair appearance and eye opening in the mouse pups. *, ** and *** represent statistically significant (*P<0.05, P<0.01 and P<0.001respectively) from* the control group; see text.

3.2. Neuromotor maturation in the developing offspring

The neuromaturation of reflexes during the weaning period of the developing pups was assessed from the day of birth PD1 until PD21. The righting, rotating, and cliff avoidance reflexes in the lithium-exposed offspring were found to be significantly and dose-dependently suppressed throughout the weaning period (Fig. 3 A – C respectively).

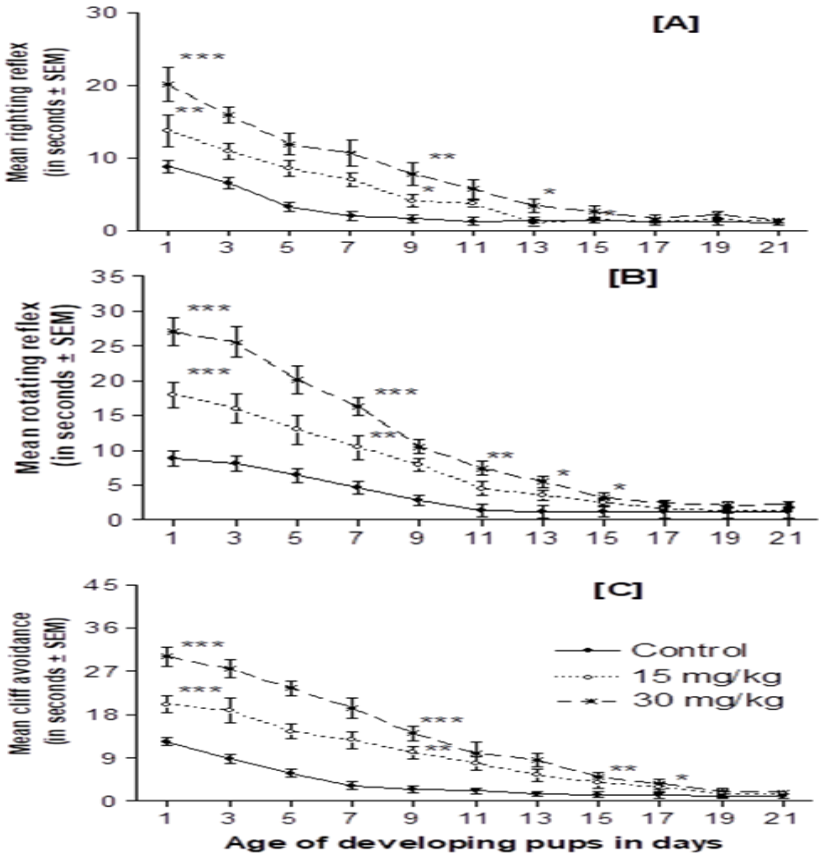

Figure 3A – C. Effect of perinatal lithium doses (15 and 30 mg/kg body weight) exposure on the dose-dependent righting reflex (A), rotating reflex (B) and cliff avoidance (C) of mouse pups during the weaning (lactation) period. *, ** and *** represent statistically significant (*P<0.05, P<0.01 and P<0.001respectively)* from the control group; see text.

3.3. Cognitive behavioral studies

3.3.1. Active avoidance test

In the shuttle-box active avoidance test, the lithium-exposed offspring (PD25), showed a statistically significant and dose-dependent decrease in the number of avoidances during the trial period as compared to the control group (Fig. 4A). The spontaneous migration of the mouse to the other compartment during trials measuring the number of crossings between the chambers when no shock was present (inter-trial crossing) showed a significant and dose-dependent decrease in the number of inter-trial crossings as compared to the controls (Fig. 4B). The total time taken during the entire trials by the animals to enter the other compartment to avoid the shock treatment (latency of avoidance response in seconds) was also measured for each animal. The results showed that the animals exposed to lithium were poor learners in a dose-dependent manner and took significant time in avoiding the shock treatment as compared to the controls (Fig. 4C).

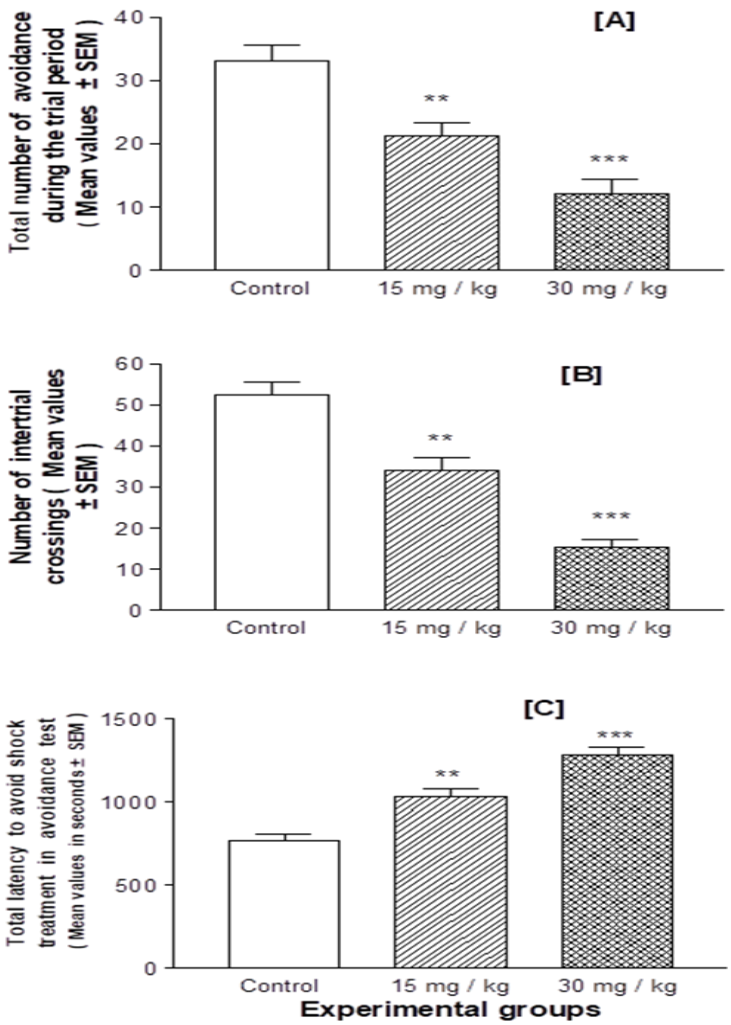

Figure 4A – C. Effect of perinatal lithium doses (15 and 30 mg/kg body weight) exposure on the dose-dependent mean performance value of the mice offspring at the age of 25 days postnatal in the active avoidance task. Mice were given a 50-trial session and the total number of times they avoided the shock by moving to the other compartment of the shuttle box (A), the number of inter-trial crossings between the chambers in the absence of current shock (B) and the total time taken by the animals (latency) to avoid the shock (C) were measured. ** and *** represent statistically significant (*P<0.01 and P<0.001respectively)* from the control group; see text.

3.3.2. Morris water-maze task

Mice offspring with lithium treatment, exhibited longer escape latencies to reach the platform as compared with the control group ($p<0.001$; Fig. 5A), however, all groups displayed a gradual improvement in performance over the 4 days of testing (training) period. The number of unsuccessful trials (failures) to reach the platform was also significantly higher in lithium treated offspring as compared to the control group on all testing days ($p<0.001$; Fig. 5B).

The probe trial studies showed that lithium exposed offspring spent more time in other three quadrants than the target (platform) quadrant as compared to the control group ($p<0.001$; Fig. 5C), in search of the platform.

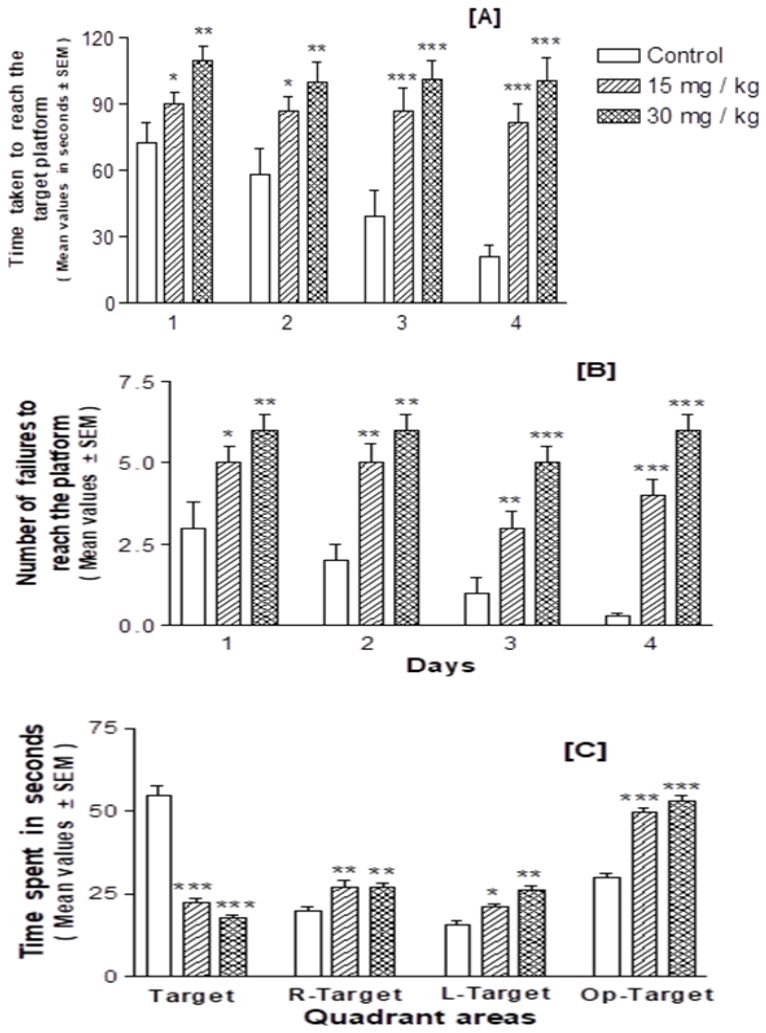

Figure 5 A – C. Performance in Morris water-maze of mice offspring at the age of 30 days postnatal whose mothers were exposed perinatally to lithium doses of 15 and 30 mg/kg body weight in a dose-dependent manner.

A – Shows the mean latency to reach the hidden platform (y-axis) on each testing day (x-axis). Animals subjected to lithium exposure were slower in finding the platform than the controls on all testing days.
B – Shows the number of failures or unsuccessful trials (y-axis) on each testing day (x-axis). Lithium exposed offspring showed maximum number of failures in finding the platform as compared to controls.
C – Shows the outcome of probe test performance. Lithium exposed offspring spent less time in the target quadrant than the control group. R-Target denotes quadrant on the right side of the target quadrant, L-Target denotes the quadrant on the left side of the target quadrant and O-Target represents quadrant opposite to the target quadrant.
*, ** and *** represent statistically significant (*P<0.05, P<0.01 and P<0.001respectively)* from the control group; see text.

3.4. Biochemical Studies

3.4.1. Levels of monoamines in forebrain

There was a significant ($p<0.001$) and dose-dependent inhibition of DA as well as 5HT levels in the forebrain of mice offspring treated with lithium as compared to the control group at the ages PD7, PD14, PD21, PD30 and PD36 (Figs. 6A and B respectively).

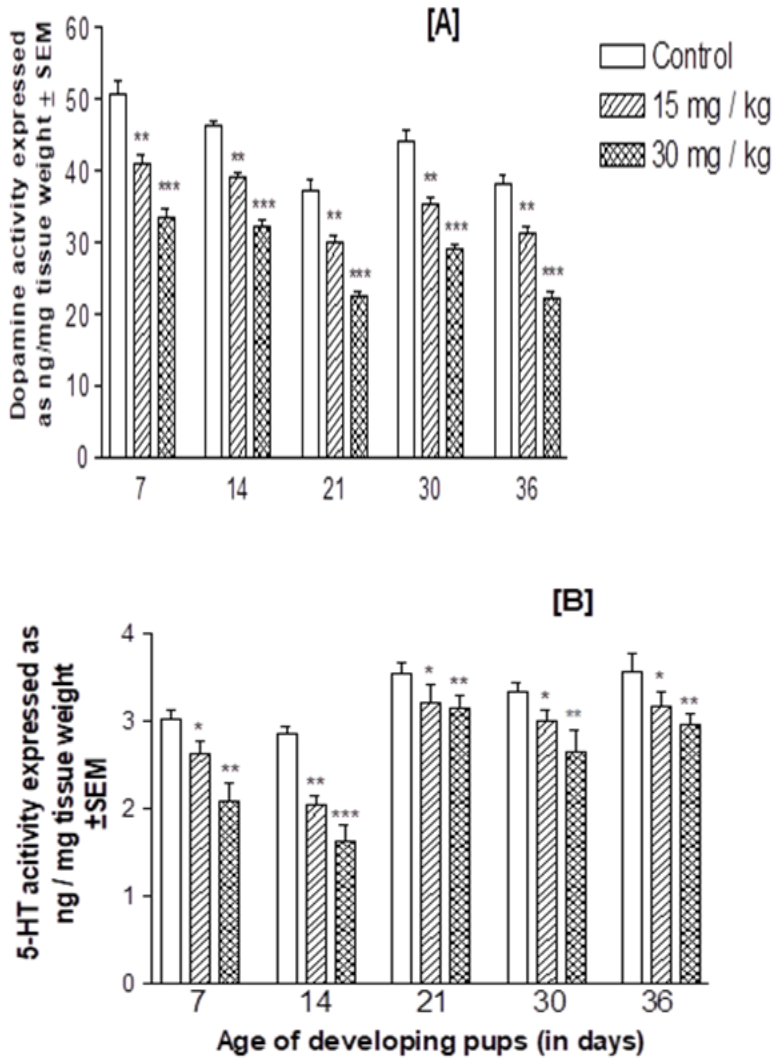

Figure 6A and B. Effect of perinatal lithium doses (15 and 30 mg/kg body weight) exposure on the dose-dependent mean levels of dopamine (A) and 5-HT (5-hydroxy-tryptamine or serotonin) (B), in the forebrain of the offspring at various postnatal developing ages (x-axis). *, ** and *** represent statistically significant (*P<0.05, P<0.01 and P<0.001respectively)* from the control group; see text.

3.4.2. Levels of non-enzymatic oxidative stress indices

LP determined as TBARS were found to be elevated significantly ($p<0.001$) due to perinatal lithium exposure in the developing forebrain of the offspring throughout the postnatal development period (PD7, PD14 and PD21) and even at adolescent ages PD30 and PD36 in a dose-dependent manner (Fig. 7A). On the contrary, reduced glutathione (GSH) level remained depleted significantly ($p<0.001$) at all developing ages in a dose-dependent manner (Fig. 7B).

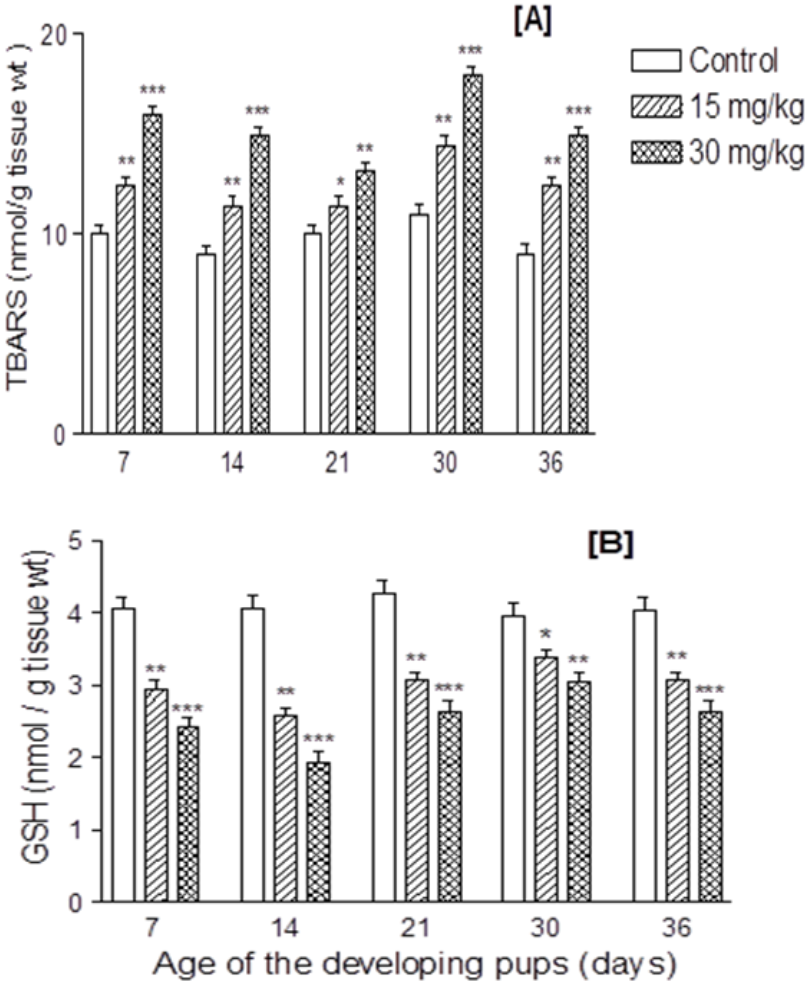

Figure 7A and B. Effect of perinatal lithium doses (15 and 30 mg/kg body weight) exposure on dose-dependent mean levels of non-enzymatic oxidative stress indices like (A) lipid peroxidation content (TBARS), and (B) total glutathione (GSH) level, in the forebrain of the offspring at various postnatal developing ages (x-axis). *, ** and *** represent statistically significant (*P<0.05, P<0.01 and P<0.001respectively)* from the control group; see text.

3.4.3. Levels of enzymatic oxidative stress indices

The levels of enzymatic OS indices GST, CAT, and SOD remained significantly

(p<0.001) depleted due to lithium in a dose-dependent manner in the fore-brain of the developing offspring at PD7, PD14, PD21, PD30 and PD36 ages (Figs. 8 A, B, and C respectively).

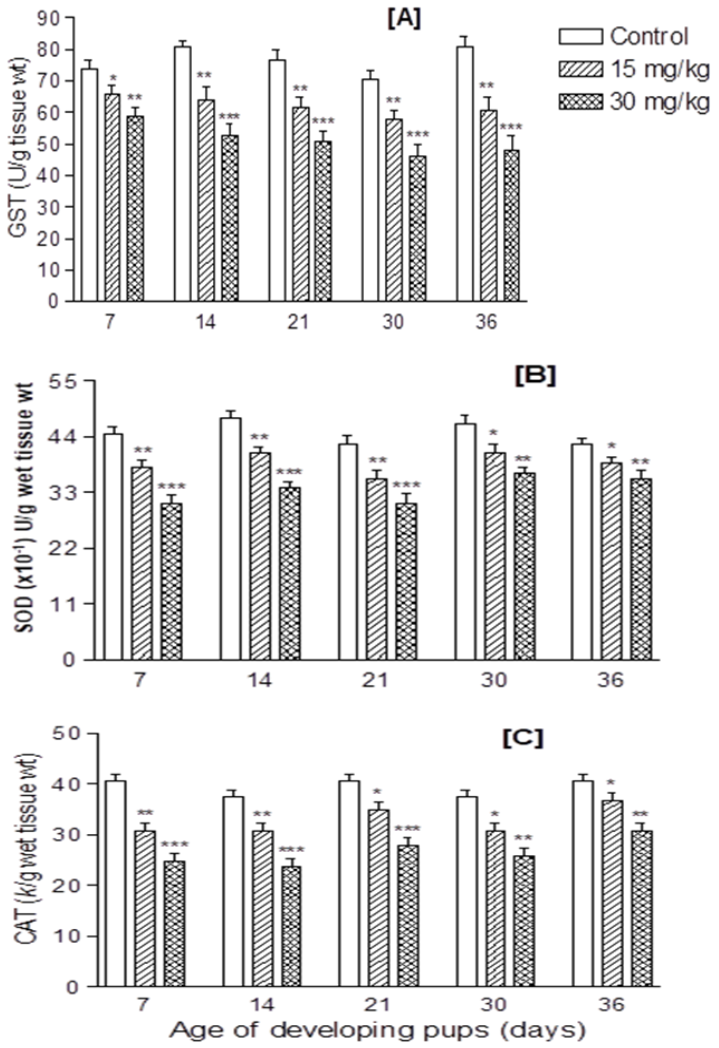

Figure 8A – C. Effect of perinatal lithium doses (15 and 30 mg/kg body weight) exposure on dose-dependent mean levels of enzymatic oxidative stress indices like (A) glutathione S-transferase (GST) level, (B) catalase (CAT) activity, and (C) superoxide dismutase (SOD) activity in the forebrain of the offspring at various postnatal developing ages (x-axis). *, ** and *** represent statistically significant (*P<0.05, P<0.01 and P<0.001respectively)* from the control group; see text.

4. Discussion

In this study, female mice exposed to lithium during pregnancy produced pups that markedly differed from their controls in the rate of physical maturation, motor reflex development at weaning age and furthermore, these pups at early post weaning and adolescent ages showed dysfunctions in active avoidance and cognitive responses and in the levels of neurotransmitters and non-enzymatic as well as enzymatic oxidative stress indices in their forebrain region. The postnatal suppression of body weight gain and the delay in opening of eyes and the appearance of body hair fuzz in the lithium exposed pups, probably indicate for a lasting effect of the prenatal lithium exposure on general growth retardation in mice offspring. Perinatal lithium administration also affected the preweaning reflexes including righting, rotating and avoiding of the cliff in the developing pups significantly as compared to the controls and the results are in agreement with earlier study (Abu-Taweel, 2012). This clearly suggests for a direct lithium intervention with the developing pups in utero because lithium ions are water-soluble and distribute throughout all of the water in the body in a manner that is similar to the distribution of sodium ions (Na+) and crosses the blood-brain barrier (BBB) easily Forester et al., 2009). Furthermore, since lithium completely equilibrates across the placenta and its passage to the newborns is also evidenced (Newport et al., 2005), our results demonstrate that mice newborns are potentially exposed to the lithium in utero through placenta. Thus, lithium exposure during fetal life does retard motor development and

physical maturation, as have been suggested in earlier studies for lithium (Abu-Taweel, 2012), and for other drugs (Brain et al., 1994) and compounds (Ajarem and Ahmad, 1998, 1991; Abu-Taweel et al., 2012).

Although, the precise mechanism of lithium toxicity still remains incompletely understood, the clinical use of lithium needs a careful and cautious attention. In spite of complications related with the level of lithium exposure around delivery period, studies related to infant follow-up are needed to have information on perinatal exposure of lithium on the offspring for understanding longer lasting effects. In this study, cognitive behavioral assessment in the offspring at post-weaning ages clearly demonstrate that perinatal exposure to lithium causes a significant longer lasting effect by inflicting cognitive dysfunction in them expressed in the form as poor learners in a dose-dependent manner taking significant longer time in avoiding the shock treatment (as in shuttle-box) and exhibiting longer escape latencies to reach the platform (as in water maze). Clinically, safe use of lithium during prenatal period and its use during lactation has been widely discouraged (American Academy of Paediatrics Committee on Drugs, 2001), and its use during late pregnancy has been associated with numerous reports of neonatal complications, like cardiac dysfunction, diabetes insipidus, hypothyroidism, low muscle tone, lethargy, hepatic abnormalities, and respiratory difficulties (Newport et al., 2005).

For cognitive functions, a number of 5-HT receptor subtypes have been reported for having different roles in the functions of serotonergic neurotransmission, including the functions connected with learning and memory processes (Petkov et al., 1995). Recently, a growing body of research has focused on the participation of serotonin (5-HT) in the neurochemical mechanisms of cognition and especially of learning and memory. As an important target organ of neurotoxicity, the hippocampus (located in the forebrain region of rodents) is a crucial element of the neurotoxicity basis of higher cognitive fonctions (Tariq et al., 2008 ; Savage et al., 2004). It is evidently suggested in the present study that the brain may be the most susceptible target organ for lithium toxicity by inhibiting the neurotransmitters DA and 5HT in the forebrain tissues in a dose-dependent manner at PD7, PD14, PD21, PD30 and PD36 ages showing a longer lasting effect of lithium.

The present study was also designed to assess the antioxidative defense system in the forebrain tissue of lithium-exposed offspring at PD7, PD14, PD21, PD30 and PD36 ages. Perinatal lithium exposure resulted in a dose-dependent and significant disturbance in the enzymatic (GST, SOD, and CAT) and non-enzymatic (TBARS and GSH) oxidative stress in the forebrain tissues. Similar lithium induced disturbances in the antioxidant barrier (involving glutathione peroxidase and superoxide dismutase) has been shown in the rat serum and tissues (Kielczykowska et al., 2004). There is ample evidence to suggest that brain tissues are highly vulnerable to the oxidative stress (Frietas, 2009) and oxidative stress has also been related with cognitive impairment (Reeta et al., 2009, 2010, 2011; Ataie et al., 2010). Thus, the cognitive dysfunction observed in the post-weaning offspring suggest for a possible strong correlation with the antioxidative defense system of the brain. Furthermore, it reflects in a way for a longer lasting effect of perinatal lithium exposure on the oxidative stress in the fore brain of the offspring.

5. Conclusion

Thus, it is concluded from the present study that females treated with lithium containing drugs during pregnancy are always at a considerable risk for several complications for their fetus. To carry out a safe treatment plan during pregnancy and/or post pregnancy (lactation) period has been a formidable challenge to the clinicians since not much experimental data is available on the perinatal risks for the newborns on teratogenic effects, direct neonatal toxicity and on long-term cognitive dysfunction and oxidative stress in brain due to perinatal lithium exposures in the newborns. The present preliminary results indicate for further advanced studies on these lines and the clinical use of lithium needs a careful and rational approach.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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