Effect Of Prenatal Lead Exposure On The Development And Behaviour of Mice Offspring .

Jamaan S. Ajarem and Gasim M. Abu-Taweel

Department of Zoology, College of Science,

King Saud University,

P.O.Box 2455, Riyadh - 11451, Saudi Arabia.

Email : jajarem@ksu.edu.sa

Abstract

Swiss-Webster strain laboratory mice were administered 'lead' at the doses of 0.1 and 0.2% (w/v) in their drinking water. Treatment started from day 1 of pregnancy and was continued until the day of delivery. The mothers were then switched to plain tap water. The treated pups showed a decline in their body weight gain from the postnatal day 1 (PD1) of their birth until PD21 throughout the weaning period. Further, the opening of their eyes and appearance of their body hairs were also delayed. A gradual suppression in the development of the early sensory motor reflexes of the treated pups was also observed. A gradual increase in the levels of total acid and alkaline phosphatases in the liver, and alterations in the acetylcholinesterase activity in the brain tissues was noticed in the developing treated offspring. Almost all behavioural indices of 'Locomotory Test' were significantly increased in the male treated offspring, except the number of wash cleaning and immobility duration, that were significantly decreased. The toxicity of lead is discussed in the light of prenatal lead exposure and the developmental stages of the treated offspring .

Key words : Prenatal ; Lead ; Fetal exposure ; Offspring ; Developmental reflexes ; Enzymes ; Locomotor behaviour .

Introduction

Although majority initiatives have been taken to reduce environmental sources of various pollutant exposure, lead (Pb) poisoning remains an important public health problem (Huang and Schneider, 2004). Pb is widespread and potentially dangerous for anyone regardless of age (Finkelstein et al., 1998; Gavaghan, 2002), however, infants and very young children are particularly vulnerable to the toxic effects of this heavy metal (Pueschel, 1974; Davis et al., 1990; Nedleman et al., 1990; White et al., 1993; Jett et al., 1997; Lanpear et al., 2000; Yang et al., 2003).

Animal studies have confirmed that exposure to low levels of Pb during early development (prenatal period) can produce long-lasting changes in the brain (Kuhlmann et al., 1977). The nervous system is the primary target for the low levels of Pb exposure and the developing brain is extremely sensitive to the toxic effects of Pb during the prenatal (gestational) period (Needleman and Gatsonis, 1990; Zawia et al., 1998; Reddy and Zawia, 2000; Chetty et al., 2001; Basha et al., 2003; Huang and Schneider, 2004, De Marco et al., 2005). Thus, chronic exposure to Pb during perinatal or early postnatal period produces central nervous system impairments as indicated by behavioural, physiological and biochemical measures (Ernhart and Greene, 1990; Lanpear et al., 2000,2001; Antonio et al., 2003; Ajarem et al., 2003). However, such studies in experimental animal models during prenatal exposure (exposure during early gestational development) is very limited (Leret et al., 2003). Thus, the aim of the present work was to study the effects of prenatal Pb exposure on the behaviour and biochemical profiles of the offspring during the early postnatal developing (weaning) period and at adolescent age.

Materials and Methods

Experimental animals :

Male and female Swiss-Webster strain laboratory adult mice were housed in opaque plastic cages (three females to one male in each cage) measuring 30 X 12 X 11 cm, in the animal facility of the Zoology Department, King Saud University, Riyadh, Saudi Arabia. Animals were kept under reversed lighting conditions with white lights on from 22.30 to 10.30 hours local time. The ambient temperature was regulated between 18 and 22° C. After pregnancy (appearance of vaginal plug was considered as day one of pregnancy), the males were removed from the cages and the females were exposed to experimental treatments. Food (Pilsbury's Diet) and water were available *ad libitum*, unless otherwise indicated .

Lead administration:

Lead acetate (analytical grade, Riedel de Haen, Germany) was dissolved in deionized distilled water in concentrations of 0.1 and 0.2% (w/v), containing 550 and 1100ppm of lead respectively. These lead doses formed the sole drinking fluid source for the experimental group of dams during the postnatal period of the experiment. The drinking fluid containing lead doses were changed with fresh preparations every five days. The control group received deionized distilled water only. In order to preclude the precipitation of insoluble lead salts, 1-2 drops of acetic

acid (vehicle of lead) were added to all bottles (including controls). No "vehicle control" group was included in this study. All pregnant mice were housed individually. Treatment of mothers was started from the day 1 of pregnancy and was continued until the day of delivery and thereafter the mothers were switched to plain deionized distilled water.

Behavioural observations :

On the day of birth (postnatal day 0, PD0) the pups were culled to only eight per dam and were left with their mothers until PD22. During this weaning period, three pups of each litter were colour 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 PD1 and repeated every other day until PD21 in the same three colour marked 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 colour marked pups per litter was considered as a single score. Thus, seven replicates from each treatment category were considered in these observations.

Body weight:

Weight is an useful indicator of development. Thus, the pups were weighed every alternate day from PD1 until PD21.

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 being set for this test.

Cliff avoidance :

Pups were placed on the edge of a table top with 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”.

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 downwards. The time elapsed until the pup rotate its body through 180° geonegatively and face its head upwards, was recorded as the rotating time. The upper limit of this test was also set at 2 min.

Eye opening and hair appearance :

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

Locomotory Tests of young adult males :

The offspring were weaned on PD21 and thereafter, only the males were isolated and kept in groups of two or three, for 14 days. Subsequently, 10 males from each treated group (including representatives from each 7 litters) were subjected to locomotor activity tests. The young adult males were placed in an experimental wooden arena measuring 80 X 80 X 30 cm and the floor was divided into 64 equal sized squares. Various behavioural elements were observed as described by Ajarem (1987). Elements of locomotory activity included the number of squares crossed and the number of wall rears as well as the duration of locomotion and immobility. The visual observations in the arena lasted 300 sec for each animal.

Biochemical Studies:

During the weaning period, on PD7, PD14, and PD21, one pup was picked up at random from each litter, apart from those three colour marked pups that were used for the behavioural tests. Thus, seven pups were collected from each experimental group on each postnatal day (PD7, 14 and 21) without any consideration to its sex and were killed by decapitation. Their brain and liver were removed and gently rinsed in physiological saline (0.9% NaCl), and then blotted on Whatman filter paper. The organ's fresh weights were recorded and were frozen.

Tissue homogenate preparation:

A 10% (w/v) homogenate of each frozen tissue was prepared in teflon-glass homogenizer at 4 ± 1°C, centrifuged at 1000 X g for 10 min. to remove cell debris and the supernatant was used for enzyme assays. The brain homogenate was prepared in an ice-cold phosphate buffer, (0.067M, pH7.2) and the liver was homogenized in chilled 0.25M sucrose solution.

Enzymes estimations:

The acetylcholinesterase (AChE) activity in the homogenized brain tissue was estimated by the method of Hestrin (1949) using acetylchloline chloride as the substrate. The specific activity of AChE was expressed as μ moles acetylcholine chloride hydrolysed per gram wet tissue weight per hour at 37 ± 1°C.

The levels of total acid phosphatase (AcP) and alkaline phosphatase (AlP) were estimated in the liver tissue homogenates using sodium p-nitrophenol phosphate as the substrate (Bergmeyer et al., 1974). The protein content in the homogenates was estimated according to the method of Lowry et al. (1951). The specific activities of these phosphomonoesterases were expressed as n-moles p-nitrophenol liberated per mg protein per minute at 37 ± 1°C.

Statistical Analysis :

The data of body weight, morphological developments, sensory motor reflexes and biochemical analyses were compared within the experimental groups by the analysis of variance (ANOVA) using minitab computer programme, and were subsequently analysed by Student’s t-test (Yamane,1973). Data of locomotory test were compared within the experimental groups by the analysis of variance (ANOVA) and subsequently were analysed using Mann-Whitney U tests (Sokal and Rohlfe,1981).

Results

The body weight of the control and treated groups of pups differed significantly right from the day of their birth. Thereafter, the mean body weight gain of the treated groups remained retarded significantly ($p<0.001$) from PD1 onwards throughout the weaning period upto PD21, in a dose-dependent manner, as compared to the controls (Fig,1).

The morphological developments, like body hair appearance and eye opening were also affected by lead treatment (Fig.2). The body hair appearance and the eye opening of the lead treated group of pups were delayed significantly ($p<0.001$), in a dose-dependent manner as compared to the controls.

Prenatal exposure of dams to lead, had a significant and dose-dependent effect on the development of all the sensory motor reflexes in the pups in the present study. Pups exposed to lead during gestational development started showing lethargic and sluggish reflexes from the first day of the birth (PD1) and onwards. Throughout the postnatal developing period, lead had a significant suppressive effect on the righting reflex ($p<0.001$) as shown in Fig.(3). The rotating reflex (Fig.4) and the cliff avoidance activity (Fig.5) in the treated pups were also significantly suppressed throughout their weaning period ($p<0.001$), upto PD21. These effects were dose-dependent and the higher dose was more suppressive affecting all the reflexes measured in the present study.

The level of AcP (Fig. 6) and AlP (Fig. 7) activities in the liver of control pups was low at PD7 stage, and increased as the weaning age of the pups increased. The liver of pups exposed to lead during the prenatal period, showed an increase in the level of these phosphomonoesterases activities at both doses of the lead, at all developing stages throughout the weaning period(Figs. 6 and 7).

The level of AChE activity increased gradually in the brain of the control pups as their weaning age increased (Fig. 8). Prenatal lead exposure at both doses, caused a biphasic influence on this enzyme at various postnatal developing stages (Fig. 8). At PD7 and PD14, the enzyme was inhibited ($p<0.001$), whereas at PD21 the enzyme was stimulated ($p<0.001$) dose-dependently.

The results of locomotor activity test (Table 1) have shown that prenatal lead exposure revealed a significant stimulatory effect. The numbers of squares crossed, wall rears and rears, in the weaned male offspring increased significantly ($p<0.001$) at the higher dose only, whereas the number of wash was significantly decreased ($p<0.001$) in the animals exposed to lead at the higher dose only, as compared to that of controls. Further, a significant ($p<0.001$) increase in the duration of locomotion and an increase in immobility duration was also observed in a dose-dependent manner (Table 1).

Discussion

The present results clearly suggest that prenatal lead exposure is extremely dangerous to the developing pups. Its effects on various aspects of brain development, biochemistry and behaviour have been examined. Gardella (2001) showed a strong coorelation between maternal and umbilical cord blood Pb levels, indicating prenatal transfer of lead from the mother to developing fetuses. In the present study, the treated pups were markedly differed from their controls in the rate of physical maturation, sensory motor development, biochemical alterations in the level of esterases in the developing liver and brain and locomotory behaviour of the young offspring. Such significant effect of lead has previously been reported in rodents (Grant et al., 1980; Draski et al., 1989; Ferguson et al.,1998 ; Antonio et al., 2003 ; Ajarem et al., 2004 ; DeMarco et al., 2005).

Prenatal lead exposure has suppressed the preweanling reflexes in the developing mice pups. The righting and rotating reflexes as well as the cliff avoidance were significantly delayed as compared to controls. Further, the effect on reflexes clearly suggests a direct intervention of lead with the developing fetus and it is likely to assume that the pups received lead via their mother's blood supply in utero. It is now well documented that significant quantities of some compounds that are given to mothers during late pregnancies and postnatal period, may be transmitted to the offspring *in utero* and /or via mother's milk during lactation (Fabro and Sieber, 1969; Mereu et al., 1987; Draski et al., 1989; Ajarem and Ahmad, 1991; 1998a and b; Ajarem, 1999; Ajarem et al., 2003).

Multiple factors are involved for the causal abnormalities in response to teratogens that ultimately induces alterations in normal cell metabolism, especially in enzymes and their substrates (Wilson, 1973), or due to combination of several factors (Coyle et al., 1976). The hepatic enzymes AcP and AlP are known good indicators of liver status (Corpas et al., 2002) and are frequently associated with transport mechanisms across the biological membranes (Starling, 1975, Ajarem and Ahmad, 1991). Thus, alterations in the level of these phosphomonoesterases in the liver of developing pups, due to prenatal lead exposure, might have led to some variations in their phosphate pool. This probably lead to disturbance in the energy source available to the animal with consequent disturbance in its metabolism (Wilson, 1973), which is reflected in the form of altered physical maturation and sensory motor rflexes.

AChE is a neurotransmitter that has been implicated in behaviour process (Allikmets, 1974). According to some authors, any change in the behaviour process due to any toxicant is indicated by some alterations in the availability of this neurotransmitter (Kruck and Pycok, 1979; Kellog et al., 1980; Lee, 1980; Bressler and Goldstein, 1991; Reddy et al., 2003). It was found in the present study that, the level of AChE in the brain of the control pups increased gradually as their weaning age increased. This may be due to the fact that a great number of brain cells (about 70%) of the closely related rats are formed after birth (Patel, 1983). Further, an inhibition in the level of AChE was detected in the lead exposed pups on PD7 and PD14. This could possibly explain as to why the sensory motor reflexes are retarded during their postnatal development. Also, it

has been established that the cerebellum in the brain may be most vulnerable to the neurotoxicity of lead in the very rapid growth period during the first 20 postnatal days (Gietzen and Wooley, 1984). Thus, lead produced developmental abnormalities in the brain as well as disturbance in the level of AChE, that might have caused the observed effects on the motor reflexes of the developing pups. It has been reported by some authors that alterations in brain enzymes are among the factors responsible for disturbances in behavioural activities of the affected animals (Branchey and Friedhoff, 1976; Kellog et al., 1980; Johnson et al., 1981; Ajarem and Ahmad, 1991; Ajarem et al.,2003).

The locomotory test on the male offspring after the weaning period, at the adolescent stage, showed a significant effect in their behavioural activities brought about by prenatal lead exposure and showing hyperactivity in their locomotory test.

The present results strongly support the earlier conclusion of Ajarem and Ahmad (1991, 1998) that the enzymes AcP , AlP and AChE could be used as convenient markers in teratological studies of adults as well as the developing pups during the weaning period. Further, the present results also support the earlier findings (Peters et al., 1994; Flora and Seth, 2000) that lead exerts neurotoxic effects by altering certain membrane bound enzymes and may cause oxidative stress which
ultimately alters the cellular processes. It may further be ascertained that the in utero developing central nervous system is a critical point of development and this prenatal period is extremely vulnerable to the toxic insult of Pb exposure which may be expressed in disturbed form of morphological development, sensory motor reflexes, biochemical and behavioural outcomes.

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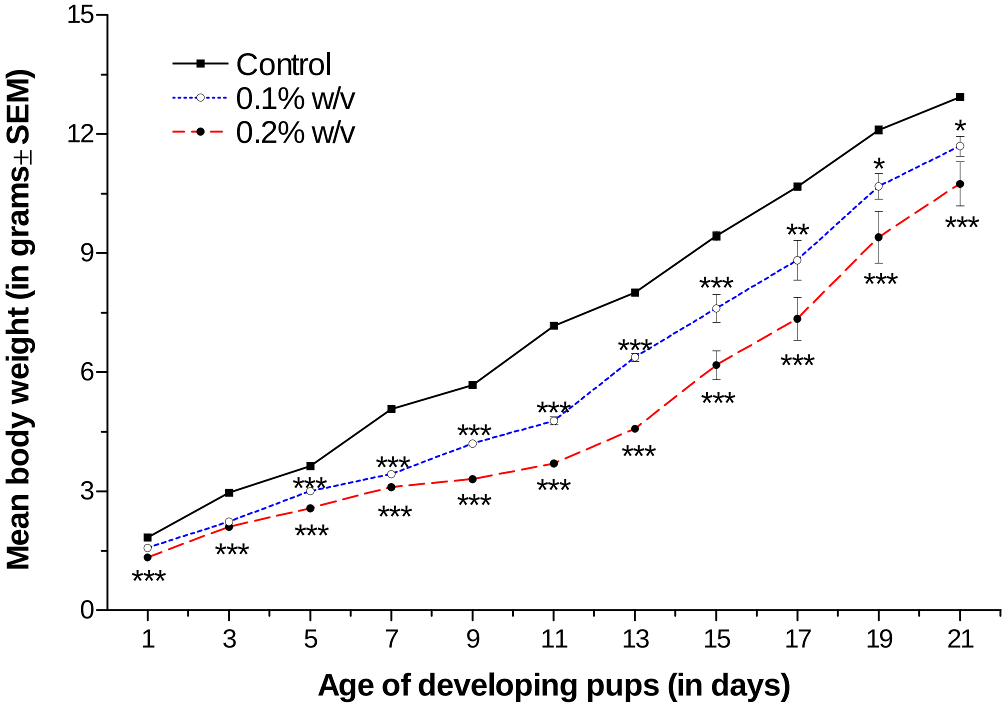

Fig. 1 : Effect of prenatal lead exposure on the body weight gain of the mouse pups.

* , ** and *** indicate significance at $p<0.05$, $p< 0.01$ and $p<0.001$, respectively, as compared to control (by Student's t-test).

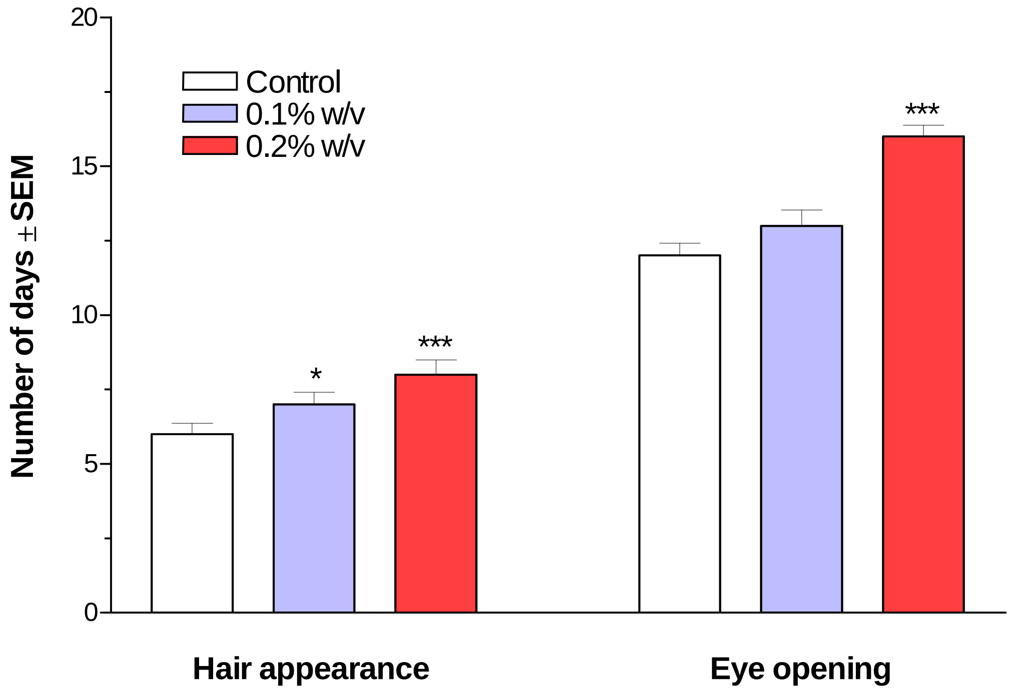

Fig. 2 : Effect of prenatal lead exposure on the hair appearance and eye opening in the mouse pups.

* and *** indicate significance at p<0.01 and p<0.001 respectively as compared to control (by Student's t- test).

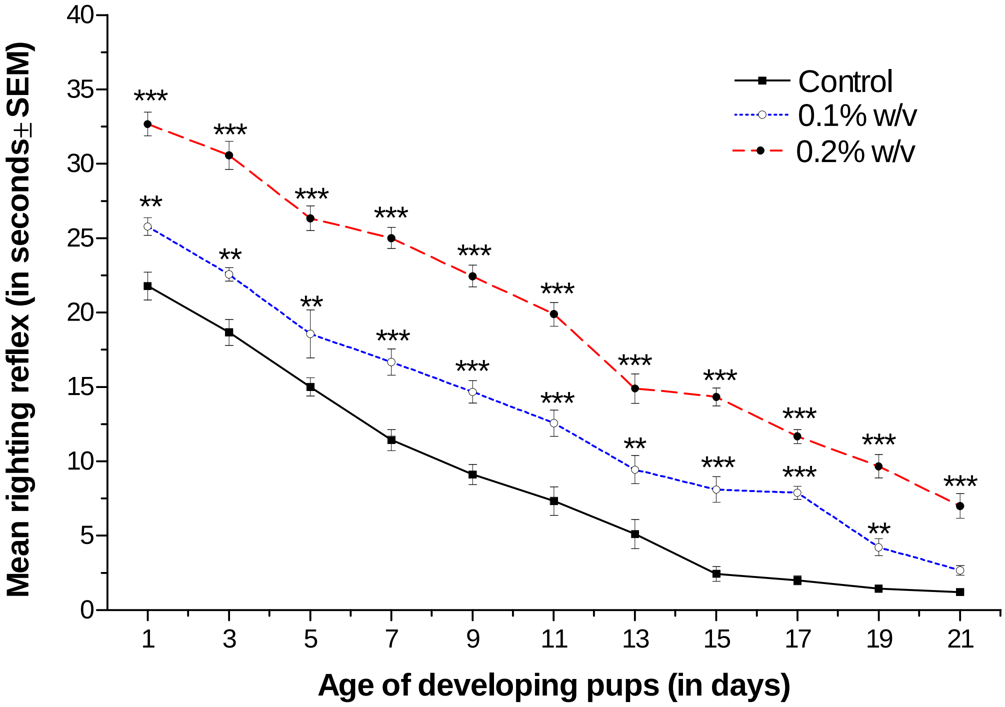

Fig. 3 : Effect of prenatal lead exposure on the mean righting reflex of the mouse pups. ** and *** indicate significance at p<0.01 and p<0.001 , respectively, as compared to control (by Student's t-test).

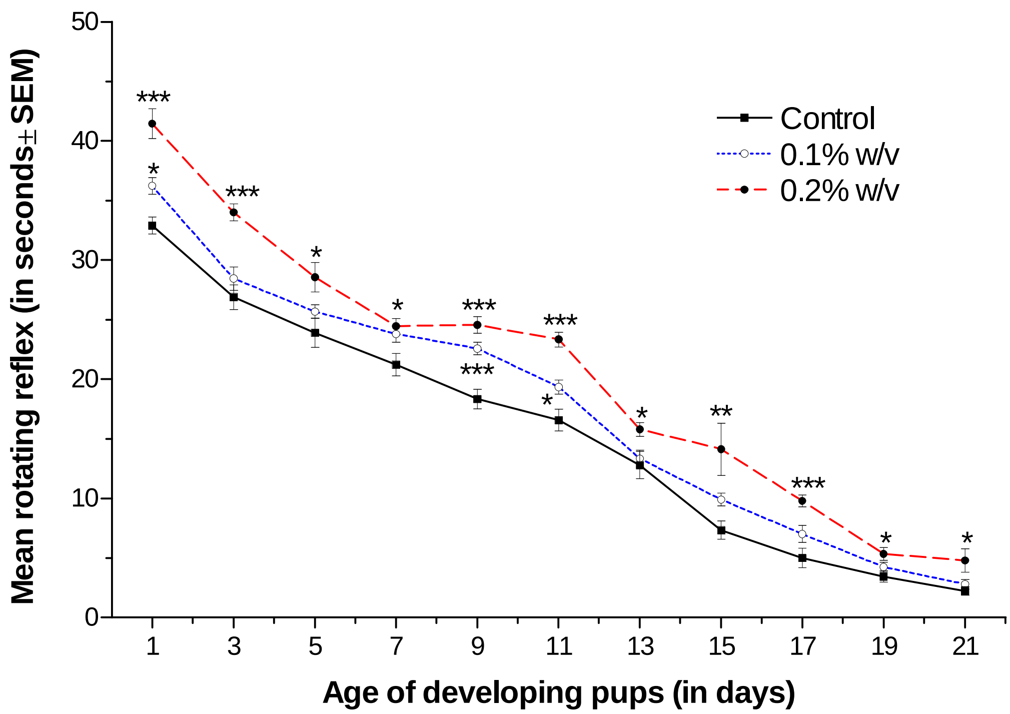

Fig. 4 : Effect of prenatal lead exposure on the mean rotating reflex of the mouse pups. *, ** and *** indicate significance at p<0.05, p<0.01 and p< 0.001, respectively, as compared to control (by Student's t-test).

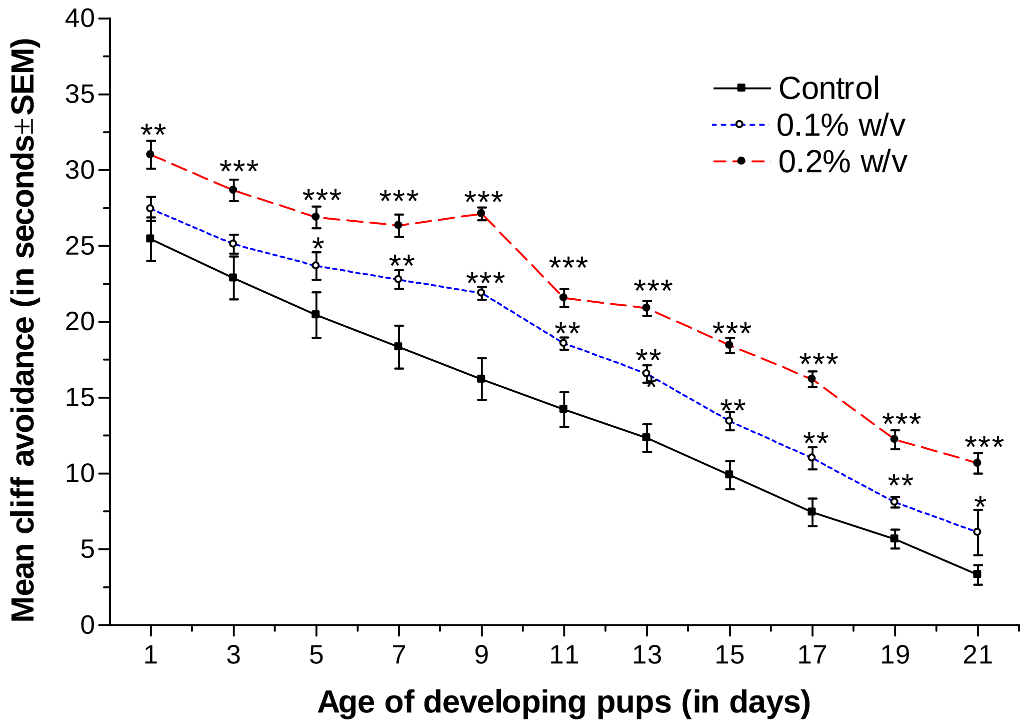

Fig. 5 : Effect of prenatal lead exposure on the mean cliff avoidance activity of mouse pups.

** and *** indicate significance at p<0.01 and p< 0.001 , respectively, as compared to control (by Student's t-test).

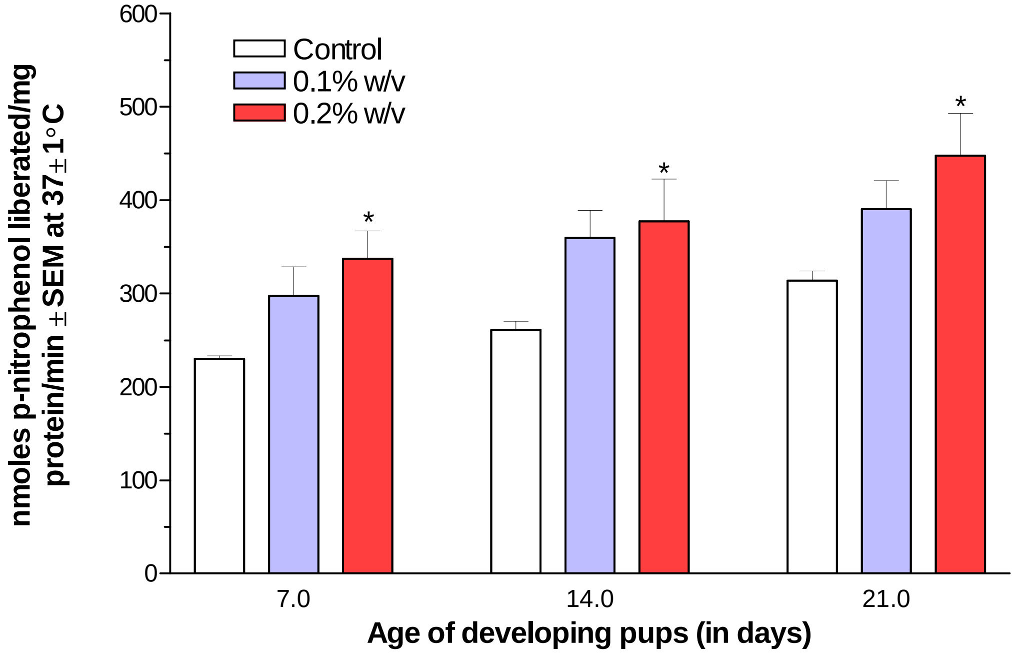

Fig. 6 : Effect of prenatal lead exposure on the activity of AcP in liver of the mouse pups at various developing weaning ages,

* indicates significance at $p < 0.001$ as compared to control (by Student's t-test).

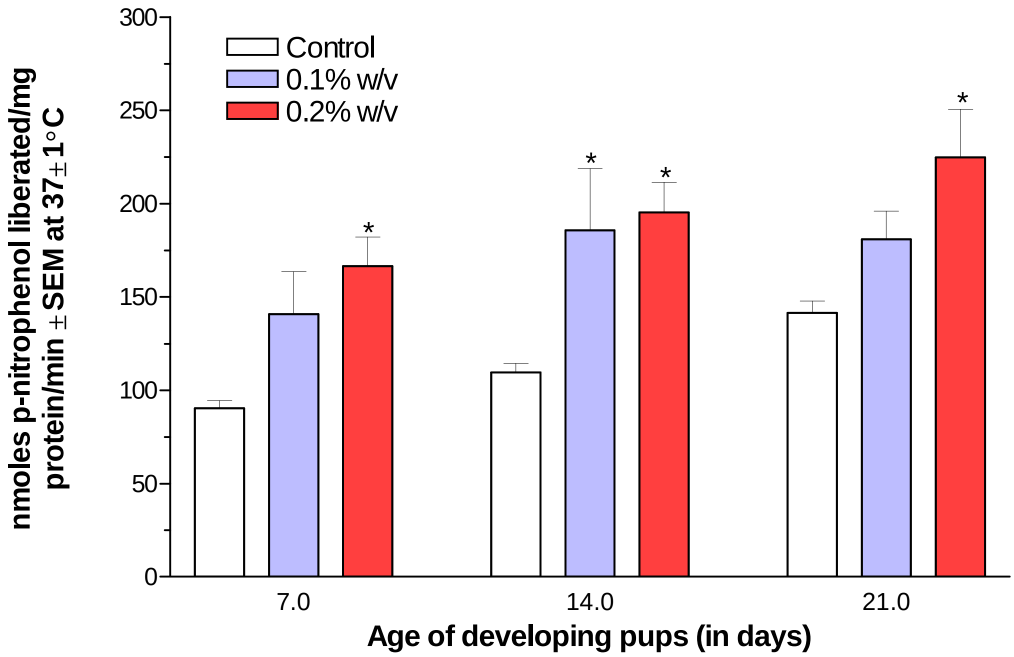

Fig. 7 : Effect of prenatal lead exposure on the activity of AlP in liver of the mouse pups at various developing weaning ages,

* indicates significance at $p < 0.001$ as compared to control (by Student's t-test).

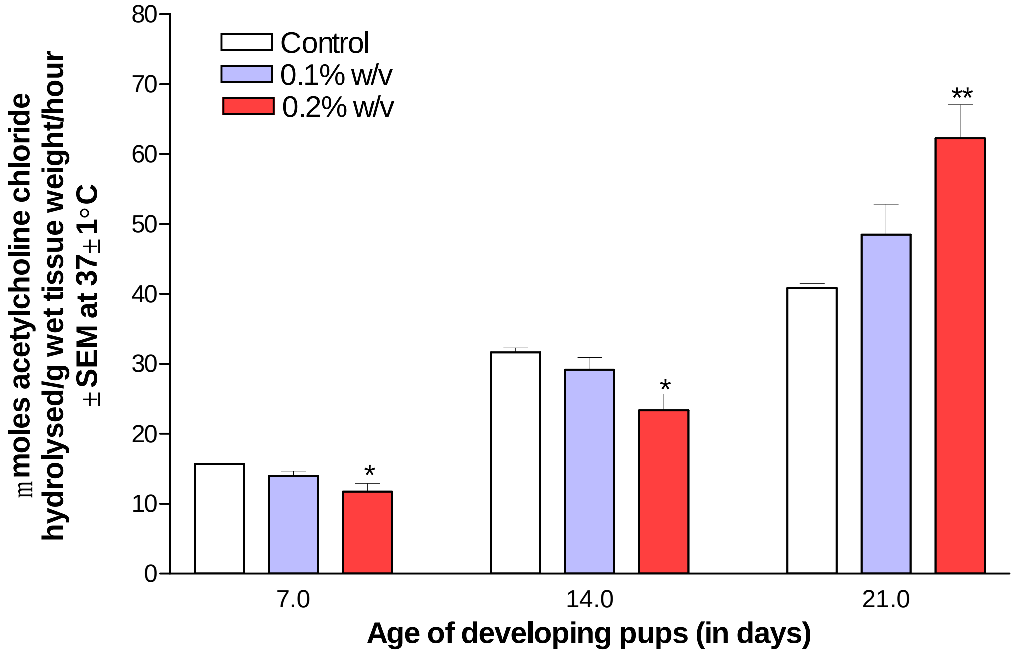

Fig. 8 : Effect of prenatal lead exposure on the activity of AChE in brain of the mouse pups at various developing weaning ages.

* and ** indicate significance at $p<0.01$ and $p< 0.001$ respectively, as compared to control (by Student's t-test).

Table 1 : Effect of prenatal lead exposure on the locomotor activity of male offspring at adolescent age .

Treatment group	Median number (with ranges) of acts and postures					
	Number of Squares crossed	Wall Rears	Rears	Wash cleaning	Locomotion Duration (sec)	Immobility Duration (sec)
Control	155 (121 - 196)	25 (15 - 36)	2 (0 - 5)	10 (0 - 21)	134.6 (88.3 - 153.3)	165.4 (147.5 - 211.7)
0.1 % w/v	190 (129 - 220)	28 (18 - 37)	3 (0 - 5)	10 (1 - 16)	163.4 * (155.6 - 159.3)	136.6 * (104.7 - 144.4)
0.2 % w/v	235 ** (173 - 240)	35 * (29 - 38)	10 ** (3 - 12)	2 * (1 - 6)	220.6 *** (199.9 - 230.7)	79.4 *** (69.3 - 100.2)

*** , ** and *** shows statistically significant at $P < 0.05$, $P < 0.01$ and $P < 0.001$ respectively from the control by Mann-Whitney U-test .**

تأثير التعرض للرصاص خلال فترة الحمل على نمو وسلوك نسل الفئران المعملية

جمعان سعيد عجارم و قاسم محمد أبو طويل
قسم علم الحيوان – كلية العلوم – جامعة الملك سعود .
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ملخص البحث : عرضت إناث الفئران المخبرية السويسرية خلال فترة الحمل إلى تراكيز مختلفة من الرصاص بنسب قدرها 0.1 % w/v ، 0.2 % w/v بالإضافة إلى المجموعة الضابطة ، وذلك عن طريق الشرب من بداية الحمل وحتى يوم الولادة ، حيث تحول الأمهات إلى ماء الشرب العادي . درست بعض الصفات المورفولوجية والسلوكية والكيموحيوية للمواليد خلال فترات النمو المختلفة إلى اليوم الحادي والعشرين بعد الولادة .

النتائج المورفولوجية تشير إلى أن المعالجة بالرصاص خلال فترة النمو المبكرة أدت إلى نقص ملحوظ في وزن الجسم ، وتأخر في ظهور الشعر ، وفي زمن تفتح الأعين وإلى تثبيط للانعكاسات الحركية الحسية المبكرة عند مقارنتها بالمجموعة الضابطة . تشير النتائج الكيموحيوية إلى أن هناك زيادة ملحوظة في مستوى نشاط إنزيم الفسفاتيز الحامضي والقاعدي في الكبد واختلافات في مستوى نشاط إنزيم الأسيتايل كولين أستريز في المخ خلال فترات مختلفة من عمر الفار . أما النتائج السلوكية فتشير إلى أن المعالجة بالرصاص خلال فترة الحمل قد أحدثت زيادة معنوية في كل من عدد المربعات المقطوعة وعدد مرات الوقوف في الهواء أو على الجدار ، كما زادت فترة زمن الحركة بينما انخفضت عدد مرات تنظيف الجسم وفترة السكون مقارنة بالمجموعة الضابطة . سمية الرصاص نوقشت في ضوء مراحل نمو المواليد .