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Neurological impact of sub-chronic lead acetate exposure on pain perception in mice

Zakiyeh Khorrami, Goudarz Sadeghi Hashjin *, Mohammad Kazem Koohi, Ali Rassouli

Department of Comparative Biosciences, Faculty of Veterinary Medicine, University of Tehran, Iran

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ABSTRACT

Lead exposure is a significant environmental health concern with potential impacts on pain perception and physiological functions. This study investigates the effects of sub-chronic lead acetate exposure on pain threshold, pain intensity, blood cortisol levels, and metabolic parameters in 24 adult male albino mice. The mice were randomly divided into three groups: a control group that received fresh water and two experimental groups that received drinking water containing lead acetate at concentrations of 5 ppm and 500 ppm over a twelve-week period. Pain perception was assessed using thermal (hot plate test) and chemical (formalin injection) pain models. Exposure to lead acetate resulted in a significant increase in the latency to thermal pain response, with delays of 52 % in the 5 ppm group and 59 % in the 500 ppm group ($P < 0.05$). Thermal pain intensity was reduced significantly by 63 % in the 5 ppm group and 82 % in the 500 ppm group ($P < 0.05$). However, changes in the onset time and intensity of chemical pain, as well as blood cortisol levels, were not statistically significant. Additionally, no significant differences in food and water intake or body weight changes were observed among the groups. These findings indicate that lead exposure can alter pain perception, with effects most pronounced in the context of thermal pain. Future research should explore lead's impact across different age groups and developmental stages, as well as its effects on specific neurotransmitter systems and receptor interactions. This research provides insights into the complex effects of lead on neurological function and highlights the importance of understanding lead's broader physiological impacts.

1. Introduction

With the advent of the industrial age and increased mining activities, environmental pollutants, including heavy metals, have become a significant threat to human health, affecting various bodily systems. Lead is one of the most prevalent environmental pollutants, found ubiquitously due to its industrial applications and natural occurrences. Despite legal restrictions on its industrial use, lead remains a major environmental contaminant [14,21,3].

This metal is widely used across various industries, including battery manufacturing, water piping, paint production, plastics, ceramics, glassmaking, electronics, and insecticide production [6]. Lead contamination arises from various sources. Soil-based lead can leach into water sources, while building paint, contaminated dust, and leaded cans contribute to environmental exposure. Food and water can also be secondarily contaminated. Additionally, cosmetics, ammunition, and occupational exposure—particularly in industries like battery and paint manufacturing—pose significant risks [15]. Lead absorption primarily occurs through the digestive system and respiration [17]. Lead exerts its toxicity through oxidative stress mechanisms, which affect cell membranes, DNA, and antioxidant defense systems. Lead toxicity targets multiple organs, including the lungs, blood vessels, brain, testes, and liver [10]. Lead exposure can cause gastrointestinal symptoms such as abdominal pain, constipation, and vomiting, commonly referred to as lead colic. It may also lead to blue-gray lines on the gums due to its reaction with hydrogen sulfide. High blood pressure is another common consequence of lead exposure. Additionally, lead poisoning impacts endocrine function, decreasing pituitary and thyroid activity in adults and inhibiting growth hormone secretion in children [17]. In humans exposed to lead, infertility, stillbirth, increased menstrual irregularities, spontaneous abortions, decreased sperm count, impaired motility, and abnormal sperm morphology have been reported [7]. Anemia is often the first clinical symptom of lead exposure [11]. Seventy to ninety percent of lead in the body accumulates in hard tissues such as bones, hair, nails, and teeth. X-rays can reveal lead accumulation as high-density rings in the ossification center of the cartilage epiphysis

* Correspondence to: Department of Comparative Biosciences, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran.
E-mail address: gsadeghi@ut.ac.ir (G.S. Hashjin).

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and diagonal lines, known as lead lines, in the diaphysis of bones [17]. Previous research has shown that lead exposure has devastating effects on nervous system development, resulting in morphological, cognitive, and behavioral deficits [14, 26,30,38]. Lead accumulation in the central nervous system is particularly concerning, with high concentrations found in the gray matter of the cerebral cortex, hippocampus, cerebellum, and medulla. Lead can cause both acute and chronic encephalopathy. Muscle weakness syndrome, or lead paralysis, may occur in individuals exposed to subacute poisoning. Additionally, lead can cross the placenta, and the fetal blood-brain barrier is permeable to lead [17]. It has been reported that the concentration of lead ions within brain tissue is not uniform, with certain areas exhibiting higher concentrations. The distribution of lead in different brain regions depends on factors such as the dosage of lead exposure, the duration of contact, and the age of the individual [1,12,34]. Neurological and behavioral changes can occur with both acute and chronic lead poisoning [14,28, 31,32]. Lead can affect inflammatory processes in the brain [10]. Among the neurological effects of lead is its impact on pain sensation. Pain is an unpleasant experience typically caused by the stimulation of free nerve endings, which occurs in response to damaging stimuli, prompting the organism to avoid these harmful factors. Free nerve endings are unencapsulated and unmyelinated receptors found throughout most areas of the body. These receptors respond to mechanical stimuli, temperature changes, and harmful chemicals. The nerve fibers then transmit pain signals to the central nervous system to help prevent further tissue damage.

Previous studies have demonstrated that lead exposure can alter the pain threshold [5,36]. It has also been shown that both age and the method used to conduct pain threshold tests significantly affect the results [19,2,30]. To evaluate pain perception, several tests have been designed, including the Flinch-Jump test, Tail-Flick test, Pinch test, Hot Plate test, and Formalin test [13,29].

Evaluating the behavioral effects of lead in humans, farm animals, and companion animals through direct experimentation is not feasible. However, conducting these experiments in other animal models can reveal mechanisms and causes of behavioral disorders. The insights gained from such studies can be extrapolated to other species, encouraging clinical researchers to explore these effects in humans and paving the way for more in-depth investigations.

The present study aimed to investigate the potential effects of subchronic lead poisoning on changes in pain sensation and response in a laboratory animal model, with the goal of potentially extrapolating these findings to behavioral disorders related to pain in humans within modern urban and industrial societies. The study assessed thermal and chemical pain sensitivity and measured cortisol levels in albino mice to explore the relationship between lead exposure and pain perception.

2. Materials & methods

2.1. Chemicals

Chemicals used in this study were purchased from the following sources: lead acetate and diethyl ether from Merck Group (Darmstadt, Germany). Formaldehyde solution from Dr. Mojalli Laboratory & Pharmaceutical Chemicals (Tehran, Iran), and 0.09 % sodium chloride solution from Aburaihan Pharmaceutical Company (Tehran, Iran).

2.2. Animal model and experimental groups

In this study, adult male mice weighing between 25 and 30 g were selected for experimentation. The mice were obtained from the Department of Laboratory Animal Breeding and Reproduction, Faculty of Veterinary Medicine, University of Tehran. They were housed in transparent polyethylene cages under controlled conditions of 12 h of light and 12 h of darkness, with a temperature maintained at 22–25°C. The animals were allowed a 10-day acclimation period before the experimental phase, during which they were kept under standard conditions with access to commercial food and municipal water.

The study adhered to ethical guidelines for laboratory animal research as specified by the Faculty of Veterinary Medicine, University of Tehran.

A total of 24 mice were randomly assigned to the following groups, with 8 mice in each group:

A. **Control Group:** Received normal drinking water.

B. **5 ppm Group**: Received drinking water containing 5 ppm of lead acetate.

C. **500 ppm Group:** Received drinking water containing 500 ppm of lead acetate.

2.3. Measurements

2.3.1. Food intake

For all groups, an equal and sufficient amount of commercial food was provided every two weeks. The food was weighed using a digital scale and made available to the animals on days 15, 29, 43, 57, 71, and 85. The amount of food consumed was calculated by subtracting the remaining food from the initial amount provided.

2.3.2. Water consumption

An equal amount of drinking water, with specific dosages of lead acetate, was provided to each group every two weeks. The control group received water without lead acetate, the second group received water containing 5 ppm of lead acetate, and the third group received water containing 500 ppm of lead acetate. The amount of water consumed was measured by calculating the difference between the initial and remaining water on days 15, 29, 43, 57, 71, and 85.

2.3.3. Weight changes

Weight measurements for each group were recorded on days 29, 43, 57, 71, and 85. Weight changes were calculated by comparing the weight of the animals on these days with their weight from the previous two weeks.

2.3.4. Assessment of Heat-Induced Pain Sensation

On the 91st day, a thermal pain sensation test was conducted for each animal. The animals were placed on a hot plate maintained (a product of Tajhizgostar Company, Tehran, Iran) at 60°C for a maximum of 20 s. The first reaction, indicated by the animal licking its paw, was recorded using a timer as a measure of the onset of pain. Additionally, the number of times the animal licked its paw within 20 s was counted as an indicator of pain intensity.

2.3.5. Chemical nociception evaluation

On the 91st day, each animal underwent a chemical nociception test. Formalin (1 %) was injected subcutaneously (0.05 ml) into the sole of the animal's right foot. The animal's reaction was monitored with a CCTV camera for 5 min. The first instance of paw licking at the injection site was recorded as an indicator of the onset of chemical pain, The duration of time the mice spent licking its paw was used as an indicator of the intensity of the chemical pain sensation.

2.3.6. Assessment of blood cortisol levels

After completing the thermal and chemical pain evaluations, blood cortisol levels were measured. The mice were anesthetized with diethyl ether and then euthanized using a guillotine. Blood samples were collected, allowed to coagulate at room temperature, and then centrifuged to separate the serum. Cortisol levels in the serum were measured in micrograms per decilitre using the ELISA method.

2.4. Statistical analysis

After conducting the experiments, data were collected, and the

mean, standard deviation, and standard error were calculated. Outliers were detected using the 1.5 IQR method. The significance of the data was assessed across different groups using one-way analysis of variance (ANOVA), followed by pairwise comparisons with the Bonferroni test. A p-value of less than 0.05 was considered statistically significant. The results were presented in graphs and tables, with data analysis and presentation performed using Excel 2010, Slide Write 7.0 Plus, and Primer Statistics software.

3. Results

3.1. Effect of lead acetate on the onset of thermal pain sensation

The average onset time of thermal pain in the control group was 11.57 s. In contrast, the onset times in the 5 ppm and 500 ppm lead acetate groups were 17.63 s and 18.38 s, respectively. Both the 5 ppm and 500 ppm groups showed a significant increase in pain onset time compared to the control group (See Fig. 1).

Note: The number of stars in the figures represents the degree of parameter changes relative to the variables. For example, * indicates a lower intensity of significant changes, while ** signifies a higher intensity.

3.2. Effect of lead acetate on the intensity of thermal pain

The average number of paw licks in response to thermal pain was 2.71 in the control group, 1.00 in the 5 ppm group, and 0.50 in the 500 ppm group. A significant decrease in paw licks was observed in the 5 ppm and 500 ppm groups compared to the control group (See Fig. 2).

3.3. Effect of lead acetate on the onset time of chemical pain

The average onset time of chemical pain was 28.43 s in the control group, 117.75 s in the 5 ppm group, and 78.88 s in the 500 ppm group. Both the 5 ppm and 500 ppm groups experienced a delayed reaction onset to chemical pain compared to the control group; however, these differences were not statistically significant. Additionally, while the 5 ppm group had a slightly longer onset time for chemical pain compared to the 500 ppm group, this difference was also not significant (See Fig. 3).

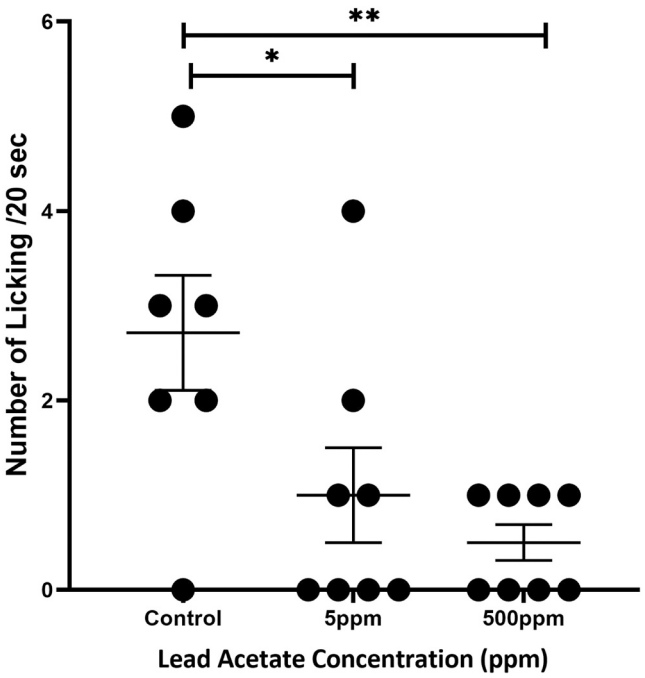

Fig. 2. Mean and standard error of thermal pain intensity in the hot plate test for the control, 5 ppm, and 500 ppm groups.

3.4. Effect of lead acetate on the intensity of chemical pain sensation

The average reaction duration to chemical pain was 72.00 s in the control group, 23.38 s in the 5 ppm group, and 49.63 s in the 500 ppm group. Both the 5 ppm and 500 ppm groups exhibited a reduced reaction duration compared to the control group, indicating a decrease in pain intensity. However, these differences were not statistically significant.

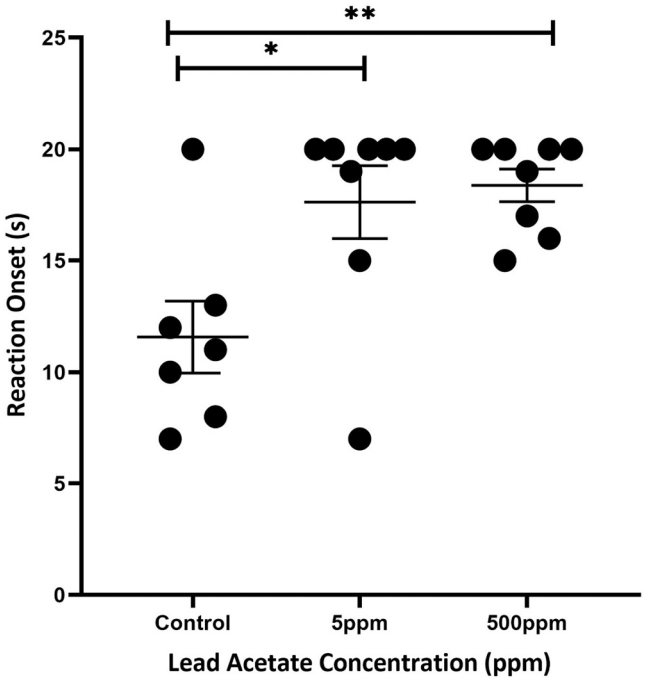

Fig. 1. Mean and standard error of the onset time for thermal pain sensation in the hot plate test for the control, 5 ppm, and 500 ppm groups.

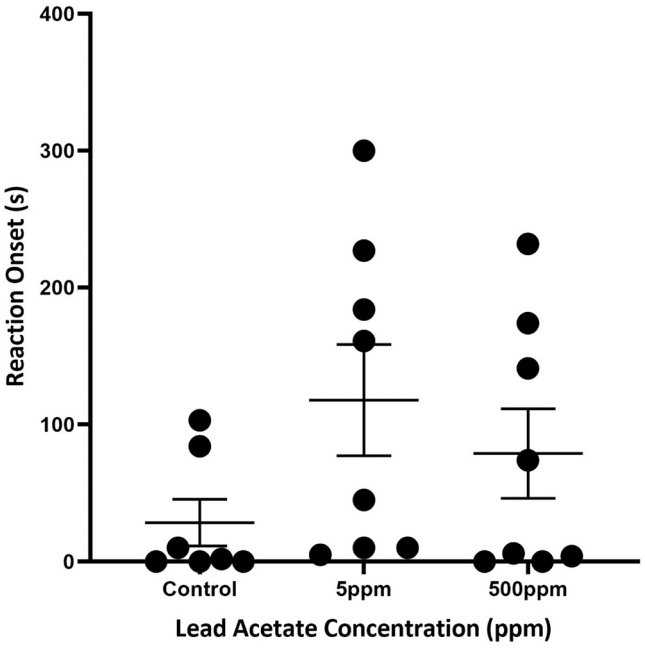

Fig. 3. Mean and standard error of the onset time for chemical pain sensation in the formalin injection test for the control, 5 ppm, and 500 ppm groups.

When comparing the 5 ppm and 500 ppm groups, the 5 ppm group showed a lower reaction duration, but this difference was also not significant (See Fig. 4).

3.5. Effect of lead acetate on blood cortisol levels

The average blood cortisol levels were 0.77 μg/dL in the control group, 0.62 μg/dL in the 5 ppm group, and 0.92 μg/dL in the 500 ppm group. The differences in blood cortisol levels among the groups were not statistically significant (See Fig. 5).

3.6. Effect of lead acetate on food intake, water consumption, and body weight

The following table summarizes the average food and water intake for each animal every two weeks, as well as the changes in average body weight over the entire twelve-week period. Results showed no significant changes between the control group and the lead-exposed groups (See Table 1).

4. Discussion

In this study, the tested mice were sub-chronically exposed to lead via ingestion, which is one of the common routes of lead exposure in humans and animals. The pain threshold was assessed using two methods: the hot plate test and formalin injection. In lead-exposed groups, a significant delay in the onset and intensity of thermal pain sensation was observed. Additionally, the exposed groups showed a decrease in pain onset and intensity of chemically induced pain, although this reduction was not statistically significant. There were no significant differences in blood cortisol levels between the control and lead-exposed groups. Similarly, no significant differences were found in food and water intake or changes in body weight.

In a study, researchers examined 41 metal industry workers with at least five years of heavy metal exposure, including lead. Significant differences were observed in standard nerve conduction tests, with the study group showing prolonged latency in sympathetic skin responses from the foot. These findings suggest that chronic co-exposure to heavy metals is associated with peripheral nerve impairment, particularly affecting small nerve fibers and temperature-dependent pain thresholds [24]. In previous study, pain perception in rats born to mothers exposed to lead was examined. The mothers received lead acetate as a solution in their drinking water. The offspring were exposed to lead for 21 days during the fetal period and until 21 days after birth, at the time of weaning. The lead acetate concentrations were 300 ppm and 1000 ppm. The tail withdrawal test in 50°C water was conducted on days 10, 21, and 30. Morphine was administered at 15, 30, and 60 min before the test at various doses. In the 300 ppm group on day 10, pain tolerance decreased compared to the control group, and lead exposure disrupted the action of morphine. The analgesic effect of morphine on days 21 and 30 was not different from the control group. It is possible that lead damages the opioid receptors in the central nervous system. This sensitivity is more pronounced at a young age than in adults [23].

Several studies have shown that stress can reduce the perception of pain [20,35]. Researchers designed an experiment to understand how lead affects the central nervous system. In this experiment, rats were exposed to lead during the fetal period and for 14 days after birth. The mothers received lead as a solution in their drinking water at doses of 300 ppm and 1000 ppm. To examine the effect of lead on opioid receptors, naloxone was used. Stress was induced using a swimming test in 20°C water. To assess pain, the tail withdrawal test in 50°C water was conducted. In animals subjected only to the stress test, lead did not affect the analgesic effect of stress. However, in animals that received naloxone in addition to stress, there was a disruption in the analgesic function of naloxone. This suggests that lead interferes with opioid mediators but does not affect non-opioid mediators [19].

In another study, the effects of different doses of lead on pain

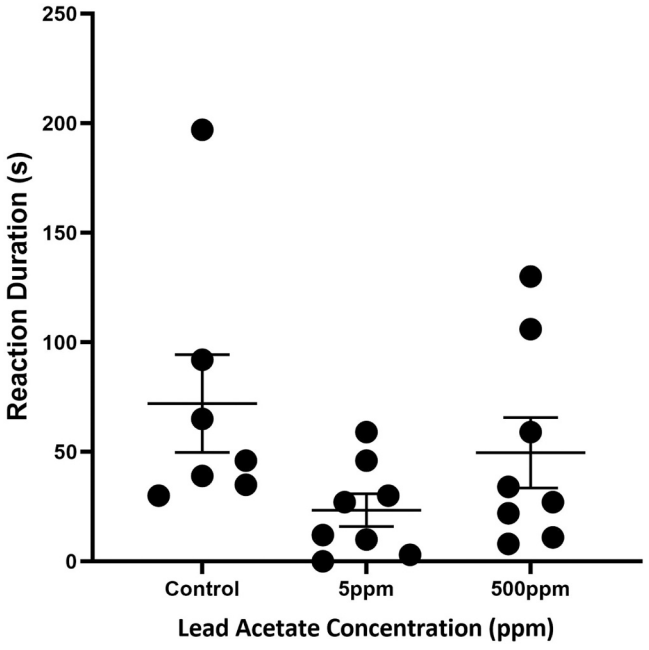

Fig. 4. Mean and standard error of chemical pain intensity in the formalin injection test for the control, 5 ppm, and 500 ppm groups.

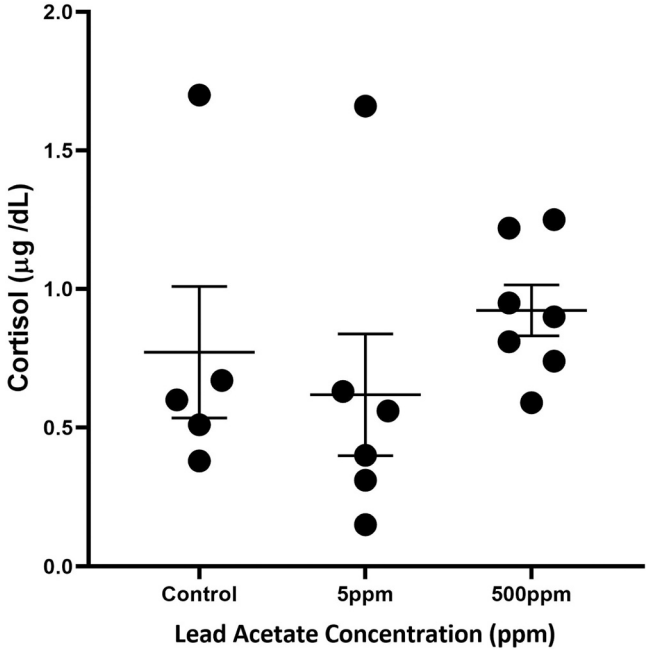

Fig. 5. Mean and standard error of blood cortisol levels in the control, 5 ppm, and 500 ppm groups.

Table 1
Comparison of food and water intake and changes in body weight in the control, 5 ppm, and 500 ppm groups.

Group	Food Intake(g/12wk)	Water Intake(ml/12wk)	Weight Gain (g/12wk)
0 ppm (Control)	64 ± 6	85 ± 7	−0.3 ± 1.2
5 ppm	68 ± 1	82 ± 6	−0.6 ± 1.3
500 ppm	58 ± 2	80 ± 5	0.2 ± 0.4

perception were investigated using male albino rats. Pain was induced via a formalin injection into the soles of their feet. The duration of paw licking was measured during two phases: 0–5 min (first phase) and 25–30 min (second phase) post-injection. Lead was administered at doses of 50, 75, 100, 125, and 150 mg/kg. In the initial phase, the duration of licking increased with doses of 50, 75, and 100 mg/kg, indicating an increase in pain. In other words, during the first phase, pain perception was not dose-dependent. However, in the second phase, lead produced analgesia that was dose-dependent [22].

The present study demonstrates that sub-chronic exposure to lead acetate alters both the threshold for pain stimulation and the intensity of pain perception. These changes were most pronounced and statistically significant regarding the onset and intensity of thermal pain. Interpreting these results is challenging due to the lack of specific neurochemical markers for diagnosing nervous system disorders. Existing literature indicates that age and gender may influence the effects of lead on the nervous system [1,30]. Another finding suggests that lead impacts various stages of neurotransmitter function, including synthesis, release, metabolism, and receptor activity [16]. It may exert its effects by disrupting the synthesis, storage, and release of endogenous opioid peptides [37]. This effect may be attributed to the impact of lead on opioid receptors [23]. This may be due to lead (Pb) accumulation in tissues, which leads to oxidative stress from excessive production of reactive oxygen species (ROS). Pb-induced oxidative stress can cause synaptic damage and neurotransmitter dysfunction, contributing to neurotoxicity [25]. It can also be assumed that the ratio of lead to calcium plays a crucial role in neurotransmitter production. Lead and calcium may compete at the neurotransmitter release sites, potentially disrupting the normal neurotransmission process [31]. Other research highlights different mechanisms through which lead may act, including the presence of specific receptors that are not related to the competitive interaction between lead and calcium [32]. It also appears that the route of lead exposure and the amount of lead absorbed play a role in these effects.

In the present study, cortisol differences among the groups were examined, and no significant effects on serum cortisol levels were observed.

Previous research has also explored the effects of lead on body hormones. One study investigated the impact of lead acetate on testosterone levels in male rats. The rats were administered lead orally for 28 days at doses of 25, 50, and 100 mg/kg. A decrease in testosterone levels was observed in the 50 and 100 mg/kg groups [27].

Additionally, research has examined the effects of lead on thyroid hormones. In a study involving albino rats, the results indicated that serum levels of T3, T4, and TSH hormones were dependent on the dose of lead exposure [33].

In another study, the effects of lead exposure on workers were investigated. The levels of cortisol, TSH, LH, T3, T4, and testosterone in the tested subjects remained within the normal range [18].

In another study investigating the association between occupational lead exposure and male reproductive hormones (MRH), an increase in serum prolactin levels was observed in exposed individuals. However, no significant differences were found in testosterone, FSH, or LH levels [4].

The results of this study indicate that changes in blood cortisol levels were not significant in cases of lead acetate poisoning. However, interpreting these results requires consideration of both the route of lead exposure and the total amount of lead absorbed by the body.

Additionally, throughout the 12-week experimental period, food and water intake, as well as body weight changes, were monitored every two weeks. No significant differences in these parameters were observed between the control group and the lead-exposed groups.

In a previous study, researchers evaluated the effect of lead on body weight. Rats were exposed to lead through their mothers during the fetal and infant stages. The study found no significant changes in body weight in the lead-exposed rats compared to the control group [37].

In another study, researchers investigated the effect of lead on weight changes. Pregnant rats were exposed to lead during pregnancy and lactation through drinking water containing lead at concentrations of 300, 600, 1000, 2000, 3000, and 4000 ppm. At higher doses, specifically 1000 ppm and above, lead exposure affected feeding behavior and weight. However, no significant effects were observed at lower doses [8].

In another study involving 299 children aged 2–3 years, an inverse association was found between detectable blood lead levels (BLLs) and body size. Children with detectable BLLs ($\geq$1 μg/dL) had a 43 % lower risk of being overweight or obese (defined as a BMI $\geq$85th percentile) and a 0.35 unit lower BMI Z-score. These findings are consistent with previous research on older children and suggest that even low-level lead exposure may influence body size in early childhood [9].

It appears that exposure to high doses of lead may lead to decreased food and water intake. Also, changes in weight and food and water intake may be influenced by factors such as genetics, age, sex, health, and route of exposure to lead.

5. Conclusion

The observed delay in response to painful stimuli following long-term lead acetate exposure suggests a potential impairment of pain's protective function. The analgesic effect of lead is not desirable, as lead is a toxic substance rather than a therapeutic one. A reduction or absence of pain perception, or a decreased reaction to pain in animals exposed to lead, is concerning. Humans or animals with a disorder may not exhibit sufficient pain responses, potentially leading to more serious, undetected issues.

This study highlights that even small concentrations of lead acetate in drinking water produce effects on pain perception comparable to those observed at higher concentrations. The reported effect not only influences physical stimuli but also suggests that lead may interfere with anaesthesia methods, potentially complicating pain management in individuals exposed to this heavy metal. Translating these preliminary findings opens the door to new research focused on the relationship between heavy metals and anaesthesia methods, particularly in populations with chronic lead exposure.

Given that exposure duration and age are critical factors in lead's effects, further studies are needed to examine these impacts across different age groups. Future research should include both laboratory animal studies and epidemiological investigations in human populations. In this study, lead was administered through drinking water, making the findings relevant to similar exposure conditions. Additional studies are recommended to investigate the effects of equivalent lead doses administered via peritoneal or intramuscular injection, allowing for comparison of pain perception across different exposure methods.

Moreover, as a complementary perspective, investigating the mechanisms related to lead's metabolism in the central nervous system may provide insights into how lead interferes with opioid receptors in peripheral nerve terminals. This line of research could elucidate the biochemical pathways underlying lead's effects on pain perception and its interactions with anaesthesia. Future studies should also include measuring lead concentrations in brain tissue and peripheral nerves to better understand its systemic and localized impacts.

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CRediT authorship contribution statement

Koohi Mohammad Kazem: Methodology. **Rassouli Ali:** Writing – original draft, Data curation. **Sadeghi Hashjin Goudarz:** Supervision. **Khorrami Zakiyeh:** Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

[1] Albores-garcia, Damaris, Jennifer L. Mcglothan, Zoran Bursac, and R. Guilarte. 2021. Neurotoxicology Chronic Developmental Lead Exposure Increases μ -Opiate Receptor Levels in the Adolescent Rat Brain 82:119–129. https://doi.org/10.1016/j.neuro.2020.11.008.

[2] Damaris Albores-Garcia, Jennifer L. McGlothan, Zoran Bursac, Tomás R. Guilarte, Chronic developmental lead exposure increases $μ$-opiate receptor levels in the adolescent rat brain, Neurotoxicology 82 (2021) 119–129.

[3] Anjum Ara, Jawed Ahmad Usmani, et al., Lead toxicity: a review, Interdiscip. Toxicol. 8 (2) (2015) 55–64.

[4] Rakesh Balachandar, Bhavani Shankara Bagepally, Ravibabu Kalahasthi, Madhumitha Haridoss, Blood lead levels and male reproductive hormones: a systematic review and meta-analysis, Toxicology 443 (August) (2020) 152574, https://doi.org/10.1016/j.tox.2020.152574.

[5] Mario Baraldi, P. Zanoli, Tiziana Rossi, Paola Borella, E. Caselgrandi, F. Petraglia, Neurobehavioral and neurochemical abnormalities of pre-and postnatally lead-exposed rats: zinc, copper and calcium status, Neurobehav. Toxicol. Teratol. 7 (5) (1985) 499–509.

[6] Basic Information about Lead in Drinking Water. 2024. US Environmental Protection Agency. 2024. http://www.epa.gov/ground-water-and-drinking-water/basic-information-about-lead-drinking-water.

[7] T.L. Bunn, J.A. Marsh, R.R. Dietert, Gender differences in developmental immunotoxicity to lead in the chicken: analysis following a single early low-level exposure in ovo, J. Toxicol. Environ. Health Part A 61 (8) (2000) 677–693.

[8] Neil G. Carmichael, Christopher Winder, Paul D. Lewis, Dose response relationships during perinatal lead administration in the rat: a model for the study of lead effects on brain development, Toxicology 21 (2) (1981) 117–128.

[9] Andrea E. Cassidy-Bushrow, Suzanne Havstad, Niladri Basu, David R. Ownby, Sung Kyun Park, Dennis R. Ownby, Christine Cole Johnson, Ganesa Wegienka, Detectable blood lead level and body size in early childhood, Biol. Trace Elem. Res. 171 (1) (2016) 41–47, https://doi.org/10.1007/s12011-015-0500-7.

[10] Karina Chibowska, Irena Baranowska-Bosiacka, Anna Falkowska, Izabela Gutowska, Marta Goschorska, Dariusz Chlubek, Effect of lead (Pb) on inflammatory processes in the brain, Int. J. Mol. Sci. 17 (12) (2016), https://doi.org/10.3390/ijms17122140.

[11] Concon, Jose M. 1988. Food Toxicology. Part A: Principles and Concepts; Part B: Contaminants and Additives.

[12] Deborah A. Cory-Slechta, Bernard Weiss, Christopher Cox, Delayed behavioral toxicity of lead with increasing exposure concentration, Toxicol. Appl. Pharmacol. 71 (3) (1983) 342–352.

[13] Stephen G. Dennis, Ronald Melzack, Samuel Gutman, Françoise Boucher, Pain modulation by adrenergic agents and morphine as measured by three pain tests, Life Sci. 26 (15) (1980) 1247–1259.

[14] Yoram Finkelstein, Morri E. Markowitz, John F. Rosen, Low-level lead-induced neurotoxicity in children: an update on central nervous system effects, Brain Res. Rev. 27 (2) (1998) 168–176, https://doi.org/10.1016/S0165-0173(98)00011-3.

[15] Lewis R. Goldfrank, S.Hoffman Robert, Goldfrank's Toxicologic Emergencies, 831, McGraw-Hill, 2006.

[16] Stefano Govoni, Maurizio Memo, L. Lucchi, P.F. Spano, M. Trabucchi, Brain neurotransmitter systems and chronic lead intoxication, Pharmacol. Res. Commun. 12 (5) (1980) 447–460.

[17] Robert A. Goyer, Thomas W. Clarkson, Toxic Effects of Metals, Casarett and Doull's Toxicology: The Basic Science of Poisons 5 (1996) 691–736.

[18] Åsa Gustafson, Andrejs Schütz Pavo Hedner, Staffan Skerfving, Occupational lead exposure and pituitary function, Int. Arch. Occup. Environ. Health 61 (1989) 277–281.

[19] Helen C. Jackson, Ian Kitchen, Perinatal lead exposure impairs opioid but not non-opioid stress-induced antinociception in developing rats, Br. J. Pharmacol. 97 (4) (1989) 1338.

[20] Helen C. Jackson, Ian Kitchen, Swim-stress-induced antinociception in young rats, Br. J. Pharmacol. 96 (3) (1989) 617.

[21] David E. Jacobs, Jonathan Wilson, Sherry L. Dixon, Janet Smith, Anne Evens, The relationship of housing and population health: a 30-year retrospective analysis, Environ. Health Perspect. 117 (4) (2009) 597–604, https://doi.org/10.1289/ehp.0800086.

[22] Theodor Kaufman, Noam Kalderon, Yehuda Ullmann, Joseph Berger, Aloe vera gel hindered wound healing of experimental second-degree burns: a quantitative controlled study, J. Burn Care \ Rehabil. 9 (2) (1988) 156–159.

[23] I. Kitchen, J. McDowell, C. Winder, J.M. Wilson, Low-level lead exposure alters morphine antinociception in neonatal rats, Toxicol. Lett. 22 (2) (1984) 119–123.

[24] Magdalena Koszewicz, Katarzyna Markowska, Marta Waliszewska-Prosol, Rafał. Poreba, Paweł. Gac, Anna Szymanska-Chabowska, Grzegorz Mazur, et al., The impact of chronic co-exposure to different heavy metals on small fibers of peripheral nerves. A study of metal industry workers, J. Occup. Med. Toxicol. 16 (1) (2021) 1–8, https://doi.org/10.1186/s12995-021-00302-6.

[25] Ju. Wook Lee, Hoon Choi, Un, Ki Hwang, Ju. Chan Kang, Yue Jai Kang, Kwang Il Kim, Jun Hwan Kim, Toxic effects of lead exposure on bioaccumulation, oxidative stress, neurotoxicity, and immune responses in fish: a review, Environ. Toxicol. Pharmacol. 68 (2019) 101–108, https://doi.org/10.1016/j.etap.2019.03.010.

[26] Lisa H. Mason, Jordan P. Harp, Dong Y. Han, Pb neurotoxicity: neuropsychological effects of lead toxicity, BioMed. Res. Int. 2014 (1) (2014) 840547.

[27] Mokhtar Mokhtari, Maryam Zanboori, The effects of lead acetate on sexual behavior and the level of testosterone in adult male rats, Int. J. Fertil. \ Steril. 5 (1) (2011) 13.

[28] Bamidele Victor Owoyele, Ahmed Olalekan Bakare, Maryam Tayo Ayinla, Kehinde Ahmed Adeshina, Damilola Onietan, Saheed O. Azeez, Antinociceptive effects of lead acetate in sciatic nerve chronic constriction injury model of peripheral neuropathy in male wistar rats, Naunyn-Schmiede's Arch. Pharmacol. 394 (2021) 117–125.

[29] Krishnaswami Ramabadran, Mylarrao Bansinath, A critical analysis of the experimental evaluation of nociceptive reactions in animals, *Pharm. Res.* 3 (1986) 263–270.

[30] Daniela Ramírez Ortega, Dinora F. González Esquivel, Tonali Blanco Ayala, Benjamín Pineda, Saul Gómez Manzo, Jaime Marcial Quino, Paul Carrillo Mora, Verónica Pérez de la Cruz, Cognitive impairment induced by lead exposure during lifespan: mechanisms of lead neurotoxicity, Toxics 9 (2) (2021) 1–30, https://doi.org/10.3390/toxics9020023.

[31] Ellen K. Silbergeld, Interactions of lead and calcium on the synaptosomal uptake of dopamine and choline, Life Sci. 20 (2) (1977) 309–318.

[32] Lidia Strużyńska, Urszula Rafałowska, The effect of lead on dopamine, GABA and histidine spontaneous and KCl-dependent releases from rat brain synaptosomes, Acta Neurobiol. Exp. 54 (3) (1994) 201–207.

[33] K. Sujatha, C. Srilatha, T.C. Rao, P. Amaravathi, Lead induced thyroid dysfunction in wistar albino rats and its amelioration with ocimum sanctum leaf extract–a hormonal and histopathological study, J. Environ. Occup. Sci. 1 (1) (2012) 12–16.

[34] Taylor, Publisher, and J.L. Domingo. 2009. Journal of Toxicology and Environmental Health: Current Issues Metal - Induced Developmental Toxicity in Mammals: A Review, no. November 2012, 37–41.

[35] Gregory W. Terman, Michael J. Morgan, John C. Liebeskind, Opioid and non-opioid stress analgesia from cold water swim: importance of stress severity, Brain Res. 372 (1) (1986) 167–171.

[36] Colin Vickers, Anna T. Paterson, Two Types Of Chronic Lead Treatment in C57BL/6 Mice: Interaction With Behavioural Determinants Of Pain, Life Sci. 39 (1) (1986) 47–53.

[37] Christopher Winder, Ian Kitchen, Lucy B. Clayton, Sue M. Gardiner, Jo.M. Wilson, Paul D. Lewis, The effect of perinatal lead administration on the ontogeny of striatal enkephalin levels in the rat, Toxicol. Appl. Pharmacol. 73 (1) (1984) 30–34.

[38] Seong Wook Yun, Heinrich Lannert, Siegfried Hoyer, Chronic exposure to low-level lead impairs learning ability during aging and energy metabolism in aged rat brain, Arch. Gerontol. Geriatr. 30 (3) (2000) 199–213, https://doi.org/10.1016/S0167-4943(00)00054-6.