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The Potential Hepatoprotective Effect of Vinpocetine against Lead-Induced Inflammatory and Apoptotic Cytokines in Rats

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Abstract

Environmental pollution with heavy metals like lead has become a matter of concern, the accumulation and multi-systemic toxicity of lead affect most body organs and its toxicity is related with many pathological changes, especially on liver. 18 Sprague-Dawley rats weighting 160-250g of both male and female were included; the animals were divided with randomness into three groups, 6 rats each group: 1st group: Rats were orally inoculated with 0.3 ml saline, after 1 hour, intraperitoneal (IP) injection of 100 µl of saline was given (Control). 2nd group: Rats received daily IP injection (20 mg/kg body wt.) of immediately preparation lead acetate for 5 days, the dose and route of administration were chose based on previous research. 3rd group Rats in this group received vinpocetine and lead as the following; at first vinpocetine administered orally by gavage tube in a dose of 3mg / kg every day for five days alone and then lead injection started in a dose of 20 mg/kg and continued for 10 days with oral vinpocetine dose where vinpocetine administered 1hr before lead. After 24 hrs (end of management period), each rat was anesthetized by diethyl ether.

Liver homogenates were done; then interleukin-1 beta (IL-1β), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α) and caspase 3 were estimated.

Lead was significantly ($P < 0.05$) raised IL-1beta, TNF-α and caspase 3, whereas it significantly ($P < 0.05$) reduced IL-10 levels. On the other hand, vinpocetine significantly ($P < 0.05$) lowered IL-1beta, caspase 3 and it significantly ($P < 0.05$) raised IL-10 but it didn't significantly ($P > 0.05$) reduce TNF-α.

Vinpocetine may have potential hepatoprotective effect against lead-induced toxicity.

Keywords: Apoptotic, Hepatoprotective, Inflammation, Lead, Vinpocetine.

الفنبوستين يوفر تأثيرًا وقائيًا للكبد ضد السيتوكينات الالتهابية والمستحثه للموت المبرمج التي يسببها الرصاص في الكبد للجرذان

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الخلاصة

أصبح التلوث البيئي بالمعادن الثقيلة مثل الرصاص مصدر قلق ، والرصاص هو مادة سامة تراكمية متعددة التاثير الضار تؤثر على أنظمة الجسم الرئيسية ؛ يرتبط بالعديد من التغييرات التي تشمل ضعف الكبد. تم تصميم هذا العمل للتحقيق في الفعالية الوقائية للفنمبوستين ضد السمية الكبدية التي تحرضها أسيتات الرصاص في الفئران. تم استخدام ثمانية عشر جرذاً بالغاً من كلا الجنسين وكانت اوزانهم تتراوح بين ١٦٠-٢٥٠غم. تم تقسيم الحيوانات بشكل عشوائي في ثلاث مجموعات من ٦ فئران لكل منها: **المجموعة الأولى**:مجموعة السيطرة. **المجموعة الثانية**: المجموعة المحفزة **المجموعة الثالثة** - فينبوسيتين ومجموعة الرصاص. وبعد قتل الفئران تم عمل متجانسات الكبد. ثم تم تقدير الانترلوكين واحد بيتا والانترلوكين عشره وعامل نخر الورم ألفا و caspase 3.

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استات الرصاص يؤدي بشكل ملحوظ (P <0.05) إلى ارتفاع الانترلوكبن واحد بيتا وعامل نخر الورم ألفا و caspase 3 ، بينما يؤدي بشكل كبير (P <0.05) إلى انخفاض مستويات الانترلوكين عشره من ناحية أخرى ، أدى فنبوستين بشكل كبير (P <0.05) إلى انخفاض الانترلوكبن واحد بيتا ، و caspase 3 وكذلك ادى بشكل ملحوظ (P <0.05) الى رفع الانترلوكين عشره ولكنه لا يقلل بشكل كبير (P> 0.05) من عامل نخر الورم ألفا.

فنبوستين له تأثير وقائي للكبد ضد السمية التي تسببها استات الرصاص في الفئران.

الكلمات المفتاحيه : الموت المبرمج ، حماية الكبد ، الالتهابات، الرصاص ، فنبوستين

Introduction

Heavy metals have considered a matter of concern for environmental pollution. one of those metals is lead. Exposition to it has become widespread because of the expanded uses of lead as building material, ceramic glazes, lead pigments, in special sort of batteries and many other utilizes [(1)]. vehicle combustion of leaded gasoline formed 90% environmental lead contamination [(2)]. There are no safe exposition levels of lead therefore it is a pivotal to control its levels in air, food, drinks that we consume [(3)]. Moreover, lead exposure has been increased 100 folds above the natural levels [(4)]. Studies detected that one third amount of lead that entered to the body stored in the liver followed by kidneys [(5,6)]. Liver is a vital organ responsible for many vital functions like production of clotting factors, nutritional processing and metabolism of cholesterol and glucose [(5)]. This accumulated lead will cause irreparable hepatocyte brutal and disrupts liver function even though chelating agents used [(5)]. The mechanism by which lead intoxicate liver is not well known but oxidative stress and transcription factors activation plus alteration of DNA may have a role [(1, 7, 8)]. Besides, inflammation may mediate a role in liver toxicities of lead [(8)], studies showed that males with high lead blood levels have leukocytosis and elevated blood levels of tissue necrosis factor- alpha [(9)]. In addition, DA KHAN and his colleagues found in occupational workers correlate the elevated inflammatory mediators with high blood levels of lead in the [(10)]

The latest treatments approved to relief hepatic intoxication with lead were often chelators such as "meso-2,3-dimercaptosuccinic acid (DMSA) and monoisoamyl DMSA (MiADMSA)", which are often toxic and fail to chelate the intracellular lead because of its hydrophilicity [(11)].

Vinpocetine have protective activity to many organs like brain, liver and heart via its voltage gated sodium and calcium channel blockade plus its antioxidant and anti-inflammatory activity. Vinpocetine is a synthetic ethyl ester of vinca alkaloid vincamine that is an alkaloid extracted from the periwinkle plant, it is well known worldwide as cerebroprotective agent contributes to improve and maintain brain functions so indicated for the treatment of memory disturbances, cognitive impairment, stroke and dementia.[10] It has an excellent safety profile, no reports of any toxicity for long-term use at a therapeutic dose up to date.[11] Vinpo is a multi-action agent with different pharmacological targets, it acts as a vasodilator, inhibitor of cyclic nucleotide phosphodiesterase 1 (PDE1), voltage-gated sodium channels, calcium channels and increases glucose and oxygen utilization in the brain. It also has anti-oxidation, anti-inflammatory, anti-thrombosis effect. [(12-16)] . This research was purposed to evaluate activity of vinpocetine against liver toxicity instigated by lead acetate in rats. which was introduced to investigate liver toxicity of lead in rat through estimation of TNF-alpha, IL-10, caspase 3 and, IL-1β in addition to the possible prophylactic role of vinpocetine against lead hepatotoxicity.

Materials and Methods

Research animals

18 rats weight 160-250g of both male and female were included in this study; the animals were acclimatized for one week before any experimental procedures. The animals were divided at random and kept at a temperature of 25+5°C while receiving commercial feed in the form of pellets and access to tap water during the experiment.

Materials

Vinpocetine (capsule 10 mg) was obtained from Americ Medic Science (USA). Lead acetate (powder) was obtained from Fluka Chemical, Turkey.

Research Design

18 Sprague-Dawley rats were divided with randomness. The first group: Rats were orally inoculated with 0.3 ml saline, after 1 hour, intraperitoneal (IP) injection of 100 µl of saline was given. This group considered as control; second group: Rats received daily IP injection (20 mg/kg body wt.) of immediately preparation lead acetate(100mg lead acetate dissolve in 20 ml N.S) for 5 days ,the dose and route of administration were chose based on previous research [(17)]. Third group: Rats in this group received vinpocetine and lead as the following; at first vinpocetine

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administered orally by gavage tube in a dose of 3mg /kg every day (dissolved in normal saline) for five days alone and then lead injection started in a dose of 20 mg/kg and continued for 10 days with oral vinpocetine dose where vinpocetine administered 1hr before lead [18-20].

After 24 hrs (end of management period), each rat was anesthetized by diethyl ether, then the homogenate was prepared from liver which was extirpated from each rat.

Homogenate preparation and estimation of biochemical parameters

After excision liver, it was rinsed with ice-cold phosphate buffer saline (pH = 7.4) in order to get rid of excess blood, then it was desiccated by utilizing filter paper and followed with quantify the liver tissue weight of each one before preparation of homogenization. After that each of rats' liver tissue hashed into tiny parts in test tube which have seize 15ml and was containing iciness phosphate buffer saline solution (pH=7.4); where (phosphate buffer saline volume (mL): tissue weight (g):) = 9:1). Homogenate was implemented by employing cell lab blender in icy circumstance. After that, the homogenate was centrifuged for about 15 min at 2000×g. until the time of TNF-α, IL1β, IL10 and caspase 3 determination. The supernatant was neatly compiled then stocked at -20 ºC. The estimation of TNF-α, IL1β, IL10 and caspase 3 were done by utilizing automated biochemistry analyzer (Elabscience, USA).

Statistical analysis

Mean± S.E.M. was used to express the results. Using an unpaired Student t-test, the significance of differences between the mean values was determined. Analysis of variance was used to compare data from various groups (ANOVA). For the data in this study, P-values less than 0.05 (P<0.05) were regarded as significant.

Results

Vinpocetine's impacts on interleukin-1beta in tissue homogenate of liver

Table 1 and Figure 1 displayed that (20mg/kg) lead acetate daily IP injection of rats for 5 days (2nd group) significantly elevated (*P*<0.05) IL-1β levels in contrast with control (1st group) rats. Mean±SEM of IL-1β in liver's tissue homogenate were sequently, 68.8±14.2and 181.7±14.

Furthermore, Table 1 as well as Figure 1 displayed that IL-1β level in liver homogenate of rats received vinpocetine plus lead (92.8±17.9 pg⁄ml) was significantly lower (P<0.05) when compared with that in rats received lead only (181.7±14 pg⁄ml).

Vinpocetine's impacts on interleukin-10 in tissue homogenate of liver

Furthermore, Table 1 and Figure 2 displayed that 20 mg/kg/day of lead acetate by IP injection for 5 days significantly reduced (P<0.05) rats IL-10 levels in group 2 (175±19.5 pg⁄ml) in comparison with rats in group 1 (384.2±13.9 pg⁄ml).Moreover, the level of cytokine IL-10 was significantly increased (302.5±14.4 pg⁄ ml, P<0.05) in liver's tissue homogenate after treatment with vinpocetine prior IP injection with lead acetate in group 3 in comparison with that in group 2 (175±19.5 pg⁄ml). as showed in Table 1 and Figure 2.

Vinpocetine's impacts on tumor necrosis factor-alpha in tissue homogenate of liver

Table 1 and Figure 3 displayed that lead acetate significantly elevated the TNF-α level (492.5±14 pg⁄ ml) in liver's tissue homogenate of group 2 (P<0.05) compared to that in group 1 (control group).

But there was no significance in lowering the levels of TNF-α in liver's tissue homogenate (*P*>0.05) for rats' group that were given vinpocetine (3mg per kg) before being injected with lead acetate (20 mg/kg) (**3rd group**). These results were compared with the result of TNF-α level in (**2nd group**) in which rats were treated with lead acetate (20 mg per kg) alone. Mean±SEM of the levels of TNF-α in liver's tissue homogenate were respectively, (492.5±14 pg⁄ ml) and (461.7±29.4 pg⁄ ml) as showed in Table 1 and Figure 3.

Vinpocetine's impacts on caspase3 in tissue homogenate of liver

Table 1 and Figure 4 displayed that there was a significant (p<0.05) elevation in caspase 3 level in liver's tissue homogenate in the group of rats intraperitoneally injected with lead acetate daily (20mg/kg) for 5 days (**2nd group**) when comparing these levels with the control (**1st group**) rats. Mean±SEM of caspase 3 in liver's tissue homogenate respectively were (7.7±0.9 pg⁄ ml) and (14.3±1.6 pg⁄ml) .

In addition, Table 1, and Figure 4 displayed that there was a significance (P<0.05) reduction in caspase 3 level in liver's tissue homogenate in the group of rats that intraperitoneally injected with lead acetate daily (20mg/kg) for 5 days plus orally administrated vinpocetine (3mg/kg) (**3rd group**) when compared with findings in group 2 in which rats were treated with lead acetate (20 mg/kg) alone. Mean±SEM of caspase 3 in liver's tissue homogenate were respectively 14.3±1.6 and 9.3±1.8.

Discussion

This research concentrates on the inflammation resulted from lead exposure. We further inspect the hepatoprotective activity of vinpocetine on these pathways. This study

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was performed to investigate activity of vinpocetine to provide anti-inflammatory and anti-apoptotic on lead-induced hepatotoxicity in rats.

It was found that lead can cause toxic effect to the hepatic tissues via inflammation and cellular apoptosis [21, 22]. IL-1β, TNF-α, caspase 3 and IL-10 are chosen in this study as measures to investigate the toxic effect of lead on liver tissues besides the IL-1β increased when there is an external inflammatory stimuli by been released; pro-inflammatory mediator or cytokine [23]. In addition, TNF-α is one of the most important mediators for inflammation produced mainly by macrophages and play a great role in (cell apoptosis and differentiation) and in the activation of immune system. Its role in inflammatory process can be summarized by "Phagocyte cell activation, endotoxic shock, Tumor cytotoxicity and cachexia" [23]. Besides, caspase 3 is a protein participate a great role in apoptosis process, its elevation can be used as an indicator for cell apoptosis and mitochondrial damage [24, 25]. On the other hand, IL-10 is an anti-inflammatory mediator released from T-cells acts by inhibition of production of cytokines and disrupts the function of mononuclear cells [23].

Agarwal et al. (2009) was pointed to predict lead toxicity to cause apoptotic effect which have observed an elevation in cytokines activity of caspase-8 and caspase-9 in most organs that include liver, kidney, and center nervous system lysates on experimental rats. This result props the lead has apoptotic effect on both pathways external and internal. [26] Also, Agarwal et al. (2009) predict the caspase series and simultaneously extracellular signal-regulated kinase (ERK) dephosphorylation are the most significant apoptotic signals which stimulated by lead acetate in rat hepatocyte stem cells Moreover, Yedjouet al. (2010) [27] set up an apoptotic-excitating agent in leukemia cells was lead also its apoptotic control role that involve excitation of caspase-3 and phosphatidyl serine externalization activation [27].

In this research lead caused significant elevation in IL-1β, TNF-α and caspase 3 levels in the hepatic tissues compared to control group, which indicates induction of inflammatory pathway in liver tissue, as shown in Table 1, and Figures 1, 3 and 4, respectively. These results are in agreement with the results of A Soussi and his colleagues [28] regarding TNF-α and caspase 3 when investigating the hepatic protective effect of vegetable oil of walnut Juglans regia against lead induced toxicity. Regarding TNF-α, our result match the elevation in hepatic tissue TNF-α after treatment with lead in the study testing the protective effect of curcumin and vitamin D against lead excited hepatotoxicity [9, 29]. Regarding IL-1β, the increased hepatic tissue levels was parallel with their elevation after treating rats with lead by W. A. Al-Megrin and his colleague to investigate the hepatic protective effect of luteolin [5].

RIL-10, the reduction in its level after treatment with lead as shown in Table 1 and Figure 2 was similar to that mentioned by Almasmoum and his colleagues who estimated the hepatic protective effect of D3 vitamin against lead excited toxicity [29].

In this study vinpoocetine may have anti-inflammatory and anti-apoptotic effect in hepatic tissues against lead induced toxicity, these activities of vinpocetine may diminish the pro-inflammatory and pro-apoptotic effect of lead on hepatic tissues. The above effect of vinpocetine can be estimated by reduction in the inflammatory mediators IL-1β, beside that vinpocetine elevated anti-inflammatory IL-10 mediator. as shown in table 1 and Figure 1,2 respectively, Vinpocetine reduced anti-apoptotic marker such as caspase 3 as shown in Table 1 and Figure 4 but vinpocetine wasn't significantly reduce TNF-α as shown in table 1 and Figure 3 that may predict need increment dose of vinpocetine above 3mg/kg to see significant effect of vinpocetine against TNF-α.

The study results are parallel with the results of S. A. Habib and his colleague, regarding reduction of TNFα and caspase 3 after treatment with vinpocetine with dose 10mg/kg and 30mg/kg to explore its hepatoprotective activity against cisplatin induced toxicity [13].

In case of IL-1β and IL-10, the changes in their hepatic tissue levels after treatment with vinpocetine was agree with that of H. F. Zaki and R. F. Abdelsalam study [14]. As a conclusion lead has hepatotoxic effect on rats represented by reduced level of IL-10 and elevated levels of IL 1beta, caspase3 and TNF alpha. In contrast vinpocetine has a protective effect on liver against lead induced toxicity by reversing the above effect. Further clinical investigations should be done in order to study vinpocetine protective effects against lead toxicity.

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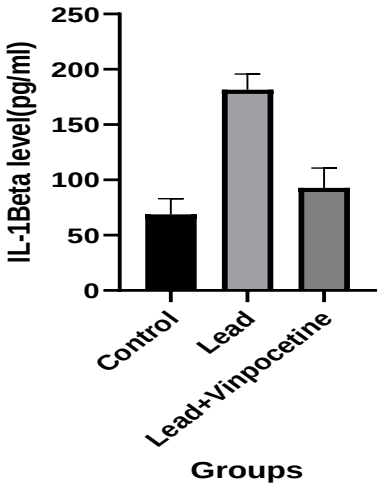

Figure 1. Effect of lead and combination of lead and vinpocetine on level of interleukin 1β in hepatic tissue homogenate of rat.

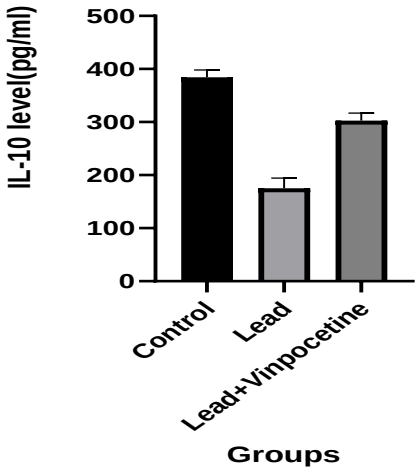

Figure 2. effect of lead and combination of lead and vinpocetine on level of interleukin 10 in hepatic tissue homogenate of rat.

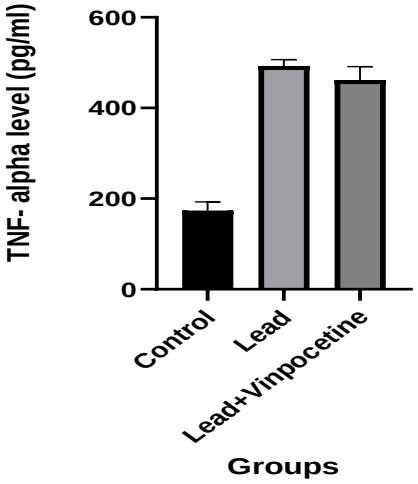

Figure 3. effect of lead and combination of lead and vinpocetine on level of TNFα in hepatic tissue.

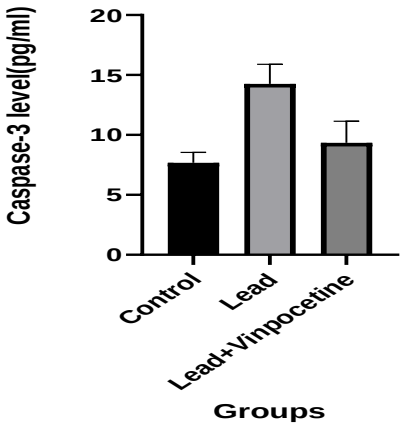

Figure 4. effect of lead and combination of lead and vinpocetine on level of caspase 3 in hepatic tissue homogenate of rat.

Table 1. Effect of vinpocetine on IL-1β, IL-10, TNF-α and caspase 3 levels in liver tissue homogenate in different study groups.

Type of treatment	IL-1β (pg⁄ml)	IL-10 (pg/ml)	TNF-α (pg⁄ml)	Caspase 3 (pg⁄ml)
Control	68.8±14.2	384.2±13.9	173.7±18.9	7.7±0.9
Lead	181.7±14 [a]	175±19.5 [a]	492.5±14[a]	14.3±1.6 [a]
Vinpocetine plus lead acetate	92.8±17.9 [b]	302.5±14.4 [b]	461.7±29.4	9.3±1.8 [b]

Values refer to mean ± standard error of means (SEM).
a Refers to significant difference ($p<0.05$) with the negative control group.
b refers to significant difference ($p<0.05$) with the positive control group (group 2) .

Conflict of Interest

The authors announced that they have no conflict of interests.

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Ethical committee

This research was approved by Scientific Research Ethical Committee at College of Pharmacy, Basrah University, Iraq.

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Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: manal and nada , sarah; data collection: and analysis and interpretation of results: noora; draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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