Prophylactic Effects of Melatonin in Lead Induced Toxicity in Rats

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الخلاصة:

يؤدي التعرض الى الرصاص الى تجمع كميات كبيرة منه في معظم الاعضاء الحيوية للجسم ولقد تم افتراض نظرية الضرر الذي تسببه الجذور الحرة كسبب وراء تلف الانسجة نتيجة التعرض للرصاص حيث تكون حالة فرط الأكسدة هي الميكانيكية المتوقعه لمثل هذا التأثير.

تم تصميم هذه الدراسة لتقييم التأثير الوقائي للميلاتونين في حالات تسمم الأعضاء المستحثة بواسطة الرصاص في الجرذان. تم تقييم تأثير الميلاتونين بهذا الخصوص على نموذج للتسمم الناتج من التعرض للرصاص في الجرذان. تم تعريض مجاميع الحيوانات التي تمت دراستها الى جرعة يومية مقدارها 100ملغم /كغم من مادة خلات الرصاص تحت الجلد لمدة شهر واحد.

تم أستخدام 20ملغم /كغم من مادة الميلاتونين عن طريق البريتون اما كعلاج مصاحب للتعرض للرصاص(وقائي).

تمت متابعة التغيرات الحاصلة في وزن جسم الحيوان، أوزان الأعضاء الحيوية الرئيسية مثل الدماغ والكبد والكلية، معايير فرط الأكسدة، محتوى الدم من الهيموغلوبين، فعالية الكبد والكليتين أضافة ألى التغييرات النسيجية التي طرأت على الأعضاء التي تمت دراستها مقارنة مع المجموعة القياسية (السلبية أوالايجابية). أظهرت النتائج بأن الميلاتونين يقي جسم الجرذان ضد الضررالذي تسببه عملية التأكسد المفرط نتيجة التعرض الى الرصاص من خلال تقليل مستويات المالونديالديهايد في الكريات الدم الحمراء، الدماغ، الكبد والكلية أضافة الى زيادة مستويات الكلوتوثايون في الأعضاء والأنسجة التي تمت دراستها؛ بالأضافة الى تحسن وظائف الأعضاء التي تمت دراستها ؛ بالأضافة الى تحسن وظائف الأعضاء التي تمت دراستها .

يمكن الأستنتاج من هذه النتائج أن الميلاتونين لـه القابلية على منع الضرر النسيجي نتيجة للتعرض الى جرع متعاقبة من خلات الرصاص وأن الحيوانات المختبرية لها القدرة على أستعادة فعالية أعضاءها الحيوية نتيجة للعلاج بالميلاتونين بعد التعرض للرصاص.

Abstract

Exposure to lead results in significant accumulation in most of vital organs, and free radical damage has been proposed as a cause of lead-induced tissue damage where oxidative stress is a likely molecular mechanism. This study is designed to evaluate therapeutic effects melatonin in lead-induced organs toxicity in rats.

Evaluation of melatonin in this respect was conducted in a rat model of lead-induced toxicity. All test groups here were challenged with subcutaneous injections of 100mg/kg lead acetate daily for one month. Melatonin in a dose of 20 mg/kg was administered intraperotoneal as adjunct treatment with lead acetate. The changes in total body weight, weight of major organs (brain, liver and kidney), oxidative stress parameters, hemoglobin content, liver and renal functions, and histological appearance of the studied organs were evaluated and compared with that of negative and positive controls. In addition, melatonin has the ability to reverse the damage induced by lead in many organs and tissues through the reduction of MDA levels in RBCs, brain, liver and kidney; and the increase in GSH levels in all studied organs; in addition to the improvement in the indices of the functions of the organs studied.

These findings demonstrate that melatonin capable of preventing damage of rat tissues caused by successive doses of lead acetate, and also demonstrate that these animals had restored their organ functions due to treatment with melatonin.

Introduction

Lead Poisoning is one of the oldest occupational hazards in the world. Despite it's recognized hazards, lead continues to have a wide spread commercial applications, including the production of storage batteries, pipes and metal alloys such as brass, solders, paints, glass and ceramics[1]. Once lead enters the body it is bound to the sulfhydryl (SH) moiety of a protein with consequent impairment of its function. By impairing the protein structure, it is unable to produce the necessary enzymes that perform certain functions [2]. Lead also interferes with regulatory mechanisms that control the metabolism of many essential cations, particularly calcium, iron, zinc, sodium and potassium. Lead also alters the integrity of the cellular and mitochondrial membranes, thereby, increasing cellular fragility and facilitate degenerative processes [3]. It interferes with many enzyme systems in the body, thereby affecting the functions of most organs [4]. Clinical manifestations of lead toxicity include symptoms referable to

the central and peripheral nervous systems, hematopoietic, renal and gastrointestinal systems. Exposure to lead has been known to adversely affect human health in urbanized communities. Lead poisoning is a potential factor in brain damage, mental impairment with severe behavioral problems, as well as anemia, kidney insufficiency, neuromuscular weakness and coma. At the molecular level, it disturbs heme biosynthesis leading to accumulation of a variety of heme precursors including δ-aminolevulinic acid (ALA) [5]. Lead has effects on the hormonal regulation of calcium absorption and lead toxicity is exacerbated in the presence of low dietary calcium. It also displaces calcium in the mineral bone matrix, which may affect bone quality. The effects on heme synthesis are the best studied toxic effects of lead, it inhibits the key enzymes, δ-ALAD and ferrochelatase (heme synthetase) [6]. As a result heme synthesis is retarded, and because heme moiety is important for the functions of cytochrome systems and cellular respiration, so lead shows an impact on the entire organism; it inhibits Na^+-K^+-ATPase pump attached to erythrocytes membrane leading to their lyses [7].

The importance of melatonin as an antioxidant depends on several characteristics: its lipophilic nature, ability to pass all bio-barriers with ease, and its availability to all tissues and cells. It distributes in all cell compartments being especially high in the nucleus and mitochondria [8]. Melatonin has also been shown to be an efficient protector of DNA [9], protein and lipids in cellular membrane [10] as well as antagonist of a number of endogenous and exogenous free radicals attach or during cellular processes [11].Thus, the spectrum of melatonin antioxidative actions is broad and it seems to be capable of efficiently counteracting oxidative stress induced by many xenobiotics including heavy metals like lead on many cell types.

Materials & Methods

Thirty six male rats (*Rattus norvegicus*) are used in the study, weighing (330-380) g, housed in the animal house of the College of Pharmacy, University of Baghdad. The animals were maintained at controlled temperature (25±2ºC) from November 2006 to April 2007, allowed free access to water, and fed standard rat chow *add libitum*.

Evaluating the prophylactic activity of melatonin, where 36 animals were allocated into 3 groups and treated as follows:

Group I, includes 12 rats injected subcutaneously (s.c) with 0.2 ml physiological saline for 30 days, and served as negative controls.

Group II, includes 12 rats injected subcutaneously (s.c) with 100mg/kg/day of lead acetate (dissolved in 0.2ml physiological saline solution) for 30 days, and served as positive controls.

Group III, includes 12 rats, exposed daily to s.c injection of 100 mg/kg lead acetate, meanwhile treated with intraperotoneal injection of 20 mg/kg/day melatonin (melatonin powder dissolved in propylene glycol then diluted with

physiological saline solution where the final concentration of propylene glycol in the solution was 1%), thirty minutes before administration of lead acetate, for thirty days.

At the end of treatment period, the rats were sacrificed by intraperotoneal injection of 100mg/kg thiopental (twenty-four hour after the last injection). Craniotomy and laparotomy were performed to obtain the brains, livers and kidneys for the assessment of tissue damage. After animals were sacrificed, blood samples were obtained by heart puncture and immediately placed into two tubes; an EDTA tube to get whole blood for the estimation of lead by atomic absorption in the Poisoning Consultation Center [(PCC), Medical City/ Baghdad], Hb, PCV, MDA and GSH in RBCs. The second fraction was transferred into plane tube to obtain the serum for analysis of other parameters (ALT, AST, ALP, Urea, and creatinine). In the plane tube, blood allowed to clot and serum was separated after centrifugation for (15-20) minutes at 2000 rpm and the resulted serum was kept frozen at (-18ºC) unless immediate analysis was indicated.

After sacrificing the animals, brains, livers, and kidneys were excised from each animal immediately, placed in chilled saline phosphate buffer solution, blotted with filter paper and accurately weighed. A 10% (W/V) tissue homogenate was prepared in phosphate buffer at 4^{o}C, using metal head tissue homogenizer which was adjusted at set 3 for one minute. All samples were kept frozen at (-18 ^{o} C) unless analyzed immediately. Specimens from the brain, liver and kidneys were prepared for histopathological examination according to the method of Bauer [157], using paraffin sections technique. The significance of differences between the mean values was calculated using unpaired student t-test and analysis of variance (ANOVA). P-values less than 0.05 were considered significant for all data presented in the results.

Results

Administration of 100mg/kg lead acetate s.c resulted in significant reduction in body weight after one month (29%) with consequent elevation of organ/body weight ratios of brain, liver and kidney; prophylactic treatment with melatonin (20 mg/kg) resulted in a significant reduction in total body weight (6%) respectively after 1 month of co-administration with lead acetate associated with restoring the organ weight/body weight ratios of the studied organs to a level still not comparable with that in controls, these levels seem to be less than that reported when lead acetate was administered alone(table-1).

Malondialdehyde levels in the RBCs, brain, liver and kidney tissues were significantly elevated after exposure of animals to 100 mg/kg lead acetate (315%, 84%, 176% and 127% respectively, $p<0.05$) compared with saline treated animals. Meanwhile, prophylactic treatment with 20 mg/kg melatonin resulted in significant decrease in MDA levels in the studied tissues (49%, 40%, 60% and 44% respectively, $p<0.05$) compared with animals challenged with lead

acetate only (table-2). Daily treatment of rats with 100 mg/kg lead acetate significantly reduces GSH levels in RBCs, brain, liver and kidney(64%, 55%, 68% and 40% respectively, $p<0.05$), compared with saline-treated animals; while prophylactic treatment with 20mg/kg melatonin, adjunct administration of lead acetate results in significant elevation of GSH in the studied tissues (90%, 89%, 181% and 35% respectively, $p<0.05$), compared with lead acetate alone treated animals(table-3). Significant decreases in Hb levels and PCV value (10% and 8% respectively, $p<0.05$) as a result of administration of 100 mg/kg lead acetate to the rats, compared with saline treated group. Meanwhile, prophylactic treatment with 20 mg/kg melatonin results in significant elevation of Hb and PCV values (7% and 5% respectively); both doses show comparable effects in this respect (table-4) compared with lead acetate treated animals. Exposure of animals to s.c injections of lead acetate (100 mg/kg) for one month produces significant elevation in the serum levels of hepatic enzymes activity (AST, ALT and ALP)(197%, 141% and 64% respectively, $p< 0.05$) compared with saline treated control animals. Meanwhile, prophylactic administration of melatonin significantly reduces enzymes activities 45%, 32% and 32% reduction was achieved with 20 mg/kg dose; the reduction in serum levels of enzymes activity was significantly different, both with respect to lead acetate only treated animal group and between each other (table-5). Lead acetate, when administered subcutaneously, in consecutive 100/kg doses for one month produces significant elevation in serum levels of urea and creatinine (98% and 167% respectively, $p<0.05$) compared with saline treated control animals. However, prophylactic treatment of another groups of animals with melatonin during lead acetate challenge, showed a significant reduction serum levels of urea and creatinine where 20 mg/kg melatonin results 24% and 23% reduction respectively; the reduction in serum levels of urea and creatinine was significantly different compared with lead acetate treated animals and between each others (table-6). Administration of lead acetate (100mg/kg) subcutaneously in rats for one month lead to significant elevation in blood lead levels (542%), and lead levels in brain, liver and kidney of these animals were also significantly elevated (3567%, 2400% and 3232% respectively, $p<0.05$) compared with saline treated animals(table -7). Prophylactic treatment of a group of animals with 20 mg/kg of melatonin through out the period of exposure to lead acetate produces a significant reduction in lead levels (blood 21%, brain 27%, liver 42%, kidney 35%) compared with lead acetate treated animals.

Treatment groups	Weight(gm)		Organ/body weight		
	Pre-treatment	Post-treatment	Brain/body ratio	Liver/body ratio	Kidney/ body ratio
Saline (n=12)	349.2±1.49 **a**	353.3±4.97 **a**	0.003±0.00008 **a**	0.029±0.0002 **a**	0.003±0.0001 **a**
Lead acetate (100mg/kg) (n=10)	347.0±1.53 **a**	246.0±9.8 **b***	0.005±0.0003 **b**	0.053±0.002 **b**	0.005±0.0003 **b**
Melatonin (20mg/kg) + lead acetate (100mg/kg) (n=10)	348.0±2.49 **a**	328.0±9.87 **d***	0.004±0.0001 **d**	0.035±0.001 **d**	0.004±0.0001 **d**

Table 1: Effects of prophylactic use of 20 mg/kg melatonin on the total body, brain, liver and kidney weights of rats challenged with 100mg/kg lead acetate for one month.

Treatment groups	Malondialdehyde (MDA)			
	RBC (nmol/g Hb)	Brain (nmol/g tissue)	Liver (nmol/g tissue)	Kidney (nmol/g tissue)
Normal saline (n=12)	6.10 ± 0.23 [a]	51.44 ± 1.88 [a]	65.16 ± 2.19 [a]	24.34 ± 1.12 [a]
Lead acetate (100mg/kg) (n=10)	25.31 ± 1.44 [b]	94.44 ± 3.05 [b]	179.93 ± 5.52 [b]	55.19 ± 2.57 [b]
Melatonin (20mg/kg) + lead acetate (100mg/kg) (n=10)	12.82 ± 1.02 [d]	56.72 ± 1.87 [d]	71.97 ± 2.21 [d]	30.91 ± 1.44 [d]

Table 2: Effects of prophylactic use of 20 mg/kg melatonin on malondialdehyde (MDA) levels in the erythrocytes, brain, liver and kidney of rats challenged with 100mg/kg lead acetate for one month

Treatment groups	Glutathione (GSH)			
	RBC (µmol/g Hb)	Brain (µmol/g tissue)	Liver (µmol/g tissue)	Kidney (µmol/g tissue)
Normal saline (n=12)	13.32 ± 0.18 [a]	11.54 ± 0.28 [a]	8.01 ± 0.28 [a]	7.57 ± 0.17 [a]
Lead acetate (100mg/kg) (n=10)	4.79 ± 0.09 [b]	5.20 ± 0.13 [b]	2.59 ± 0.06 [b]	4.52 ± 0.10 [b]
Melatonin (20mg/kg) + lead acetate (100mg/kg) (n=10)	9.10 ± 0.32 [d]	9.83 ± 0.24 [d]	7.28 ± 0.16 [d]	6.10 ± 0.16 [d]

Table 3: Effects of prophylactic use of 10 or 20 mg/kg melatonin on glutathione (GSH) levels in the erythrocytes, brain, liver and kidney of rats challenged with 100mg/kg lead acetate for one month.

Treatment groups	Hb (mg/dl)	PCV %
Saline (n=12)	14.42 ± 0.17 [a]	41.83 ± 0.68 [a]
Lead acetate (100mg/kg) (n=10)	12.96 ± 0.15 [b]	38.3 ± 0.40 [b]
Melatonin (20mg/kg) + lead acetate (100mg/kg) (n=10)	13.82 x 0.26 [c]	40.40 ± 0.75 [c]

Table 4: Effects of prophylactic use of 20 mg/kg melatonin on hematological parameters of rats challenged with 100mg/kg lead acetate for one month.

Treatment groups	Enzyme activity		
	AST (U/L)	ALT (U/L)	ALP (U/L)
Normal saline (n=12)	37.55 ± 2.09 [a]	53.46 ± 1.90 [a]	106.15 ± 2.61 [a]
Lead acetate (100mg/kg) (n=10)	111.65 ± 3.51 [b]	128.78 ± 3.91 [b]	173.56 ± 3.41 [b]
Melatonin (20mg/kg) + lead acetate (100mg/kg) (n=10)	61.11 ± 2.08 [d]	88.16 ± 2.37 [d]	117.93 ± 3.04 [d]

Table 5: Effects of prophylactic use of 20 mg/kg melatonin on the serum levels of liver enzymes activities (AST, ALT, ALP) of rats challenged with 100 mg/kg lead acetate for one month.

Treatment groups	Serum urea (mmol/L)	Serum creatinine (µmol/L)
Normal saline (n=12)	6.21 ± 0.19 [a]	75.36 ± 1.58 [a]
Lead acetate (100mg/kg) (n=10)	12.27 ± 0.43 [b]	201.55 ± 7.30 [b]
Melatonin (20mg/kg) + lead acetate (100mg/kg) (n=10)	9.31 ± 0.32 [d]	155.58 ± 6.04 [d]

Table 6: Effects of prophylactic use of 20 mg/kg melatonin on the serum levels of urea and creatinine of rats challenged with 100 mg/kg lead acetate for one month.

Treatment groups	Lead level			
	Blood (µg/dL)	Brain (µg/g tissue)	Liver (µg/g tissue)	Kidney (µg/g tissue)
Normal saline (n=12)	13.15 ± 0.44 [a]	1.07 ±0.04[a]	5.91 ± 0.22 [a]	7.98 ± 0.26 [a]
Lead acetate (100mg/kg) (n=10)	84.47 ± 2.78 [b]	39.24 ± 2.67 [b]	147.72 ± 6.10 [b]	265.87 ± 9.60 [b]
Melatonin (20mg/kg) + lead acetate (100mg/kg) (n=10)	66.56 ± 2.63 [d]	28.61 ± 1.73 [c]	85.14 ± 3.00 [d]	172.22 ± 3.86 [d]

Table 7: Effects of prophylactic use of 20 mg/kg melatonin on blood and tissue lead levels of rats challenged with 100mg/kg lead acetate for one month.

Data were expressed as mean ± SEM; n= number of animals; values with non-identical superscripts (a, b, c, d) within the same tissue were considered significantly different ($P<0.05$).

Tissue sections prepared from livers of rats treated with saline only as control group showed liver tissue with normal architecture, showing the central hepatic vein and arrangement of hepatocytes around it (figure -1). Other tissue sections (figure -2) prepared from livers of lead acetate-treated rats showed liver tissue with a marked degenerative necrosis of hepatocytes with infiltration of inflammatory cells. Pre-treatment of rats with 20 mg/kg melatonin improves the histological changes after administration of lead acetate, where the liver tissue sections showed a mild necrosis of hepatocytes and lower level of infiltration with inflammatory cells (figure -3).

Tissue sections prepared from kidneys of rats treated with saline only showed renal tissue with normal histological appearance (normal glomeruli and tubules) (figure -4).

Meanwhile, tissue sections prepared from kidneys of rats treated with 100 mg/kg lead acetate showed renal tissue with moderate degenerative changes and necrosis of the lining epithelium with inflammatory cells infiltration (figure -5). Pre-treatment of rats with 20 mg/kg melatonin before administration of lead acetate resulted in appearance relatively regenerated tubules with presence of chronic inflammatory cells (figure -6).

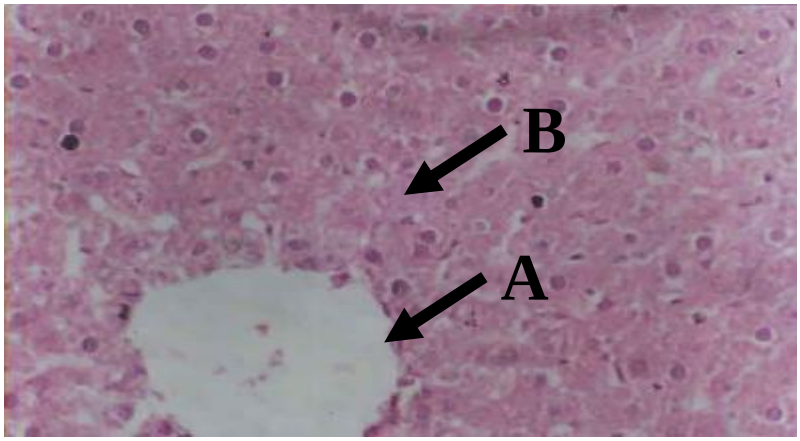

Figure 1: Section showing liver tissue with normal architecture showing the central hepatic vein (arrow A) and arrangement of hepatocytes around it (arrow B) in rats treated with normal saline for one. Magnification: 200X, (hematoxylin and eosin stain).

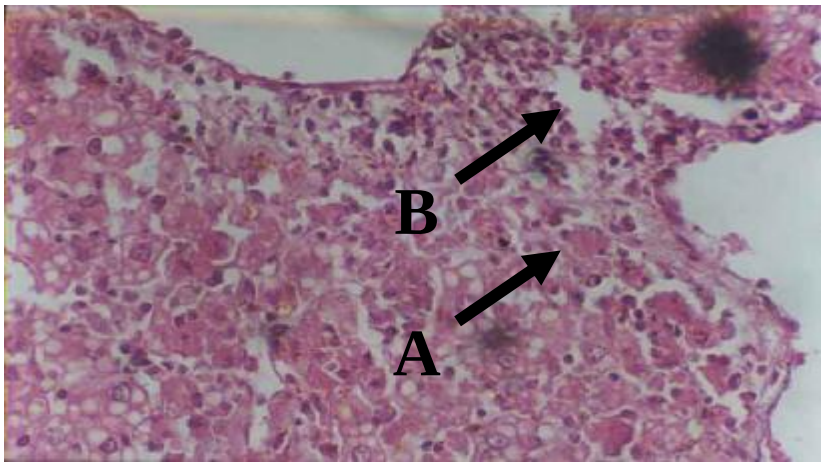

Figure2: Section showing liver tissue with a marked degenerative necrosis of hepatocytes (arrow A) with infiltration of inflammatory cells (arrow B) in rats challenged with 100mg/kg lead acetate for one month. Magnification: 200X, (hematoxylin and eosin stain).

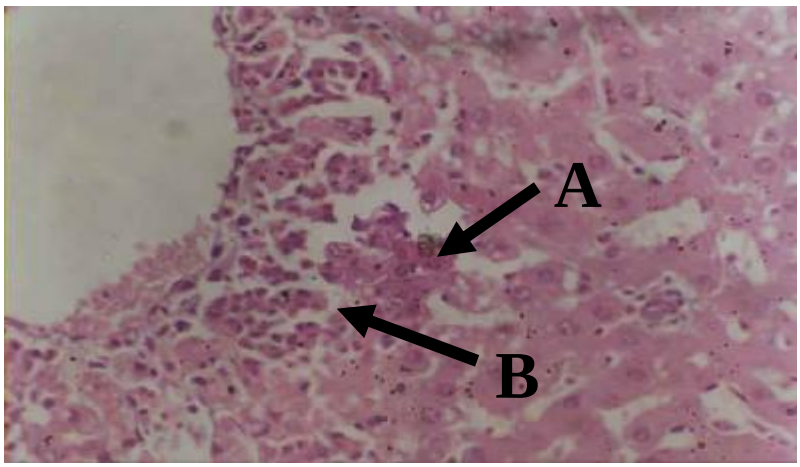

Figure 3: Section showing liver tissue with a mild necrosis of hepatocytes (arrow A) and lower level of infiltration with inflammatory cells (arrow B) in rats treated with 20 mg/kg melatonin and lead acetate 100mg/kg for one month. Magnification: 200X, (hematoxylin and eosin stain).

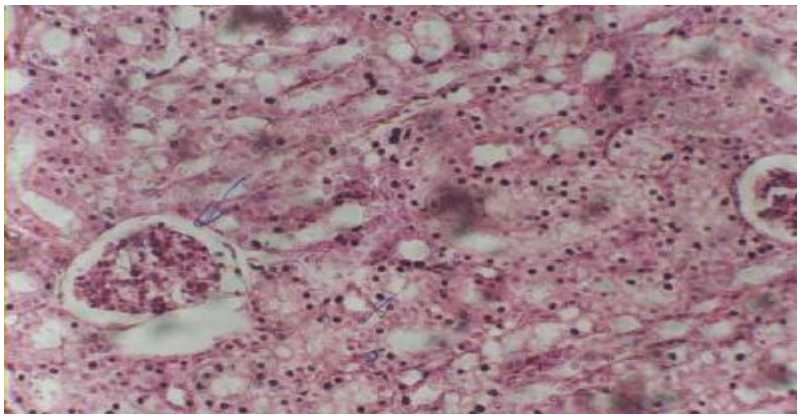

Figure 4: Section showing kidney tissue with normal histological appearance, which consists of glomeruli (arrow A) and tubules (arrow B) in rats treated with normal saline for one month. Magnification: 200X, (hematoxylin and eosin stain).

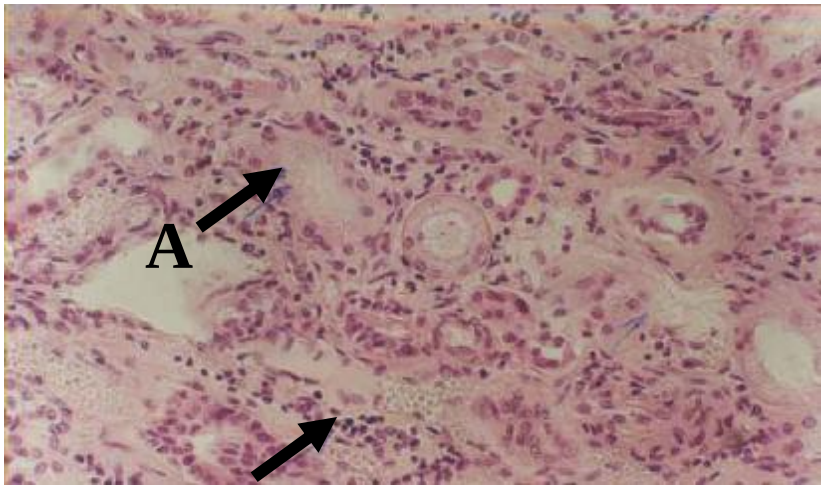

Figure 5: Section showing kidney tissue with moderate degenerative changes and necrosis of the lining epithelium (arrow A) with inflammatory cells infiltration (arrow B) in rats challenged with 100mg/kg lead acetate for one month. Magnification: 200X, (hematoxylin and eosin stain).

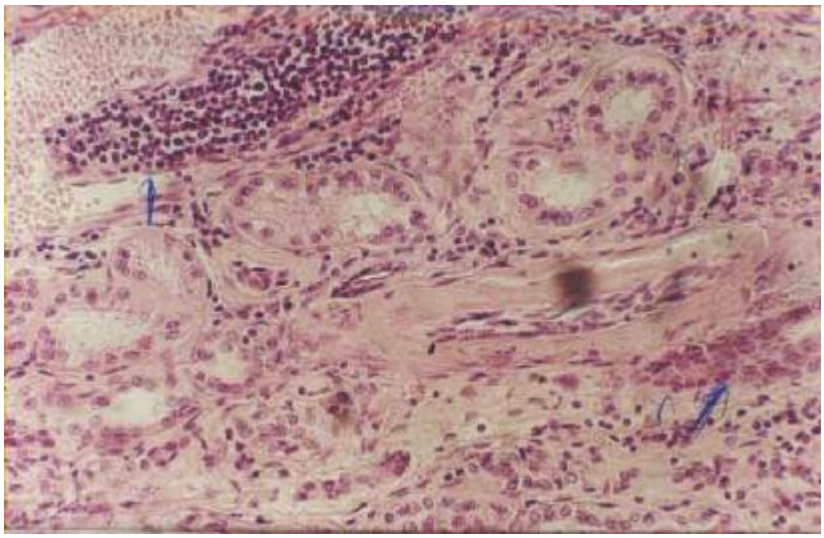

Figure 6: Section showing kidney tissue with relatively regenerated tubules (arrow A) with still presence of chronic inflammatory cells (arrow B) in rats treated with 20 mg/kg melatonin and 100mg/kg lead acetate for one month. Magnification: 200X, (hematoxylin and eosin stain).

Discussion

Daily administration of 100 mg/kg lead acetate to rats, reduce their total body weights compared with control animals with subsequent elevation of organ/body weight ratios, and treatment with melatonin restores body weights and impaired organ/total body weight ratio. Lead poisoning is very well known to affect numerous organ systems, and is associated with a number of morphological, biochemical and physiological changes that include kidney dysfunction, impaired glucose metabolism, CNS disturbances, impairment of liver function and hematological disorders [12]. Among their effects, the impaired glucose metabolism is considered as a major pathway that may be followed by changes in total body or organ weights; in this respect intoxication with lead reduces the rate of glucose metabolism, with consequent reduction of the required energy for many anabolic process [13], and the profound decrease in serum glucose level which is reported in rabbits intoxicated with lead, might also be a cause for tissue wasting due to inappropriate availability of energy. The findings of the present study are found compatible with those reported by others [14], where loss of total body weight is found parallel with the increase in blood lead levels; furthermore, the increase in oxidative stress exhibited contributing factor, where lipid peroxidation might predispose to perturbation in the content of lipids in many organs and tissues. Exposure to lead acetate significantly elevates MDA levels in erythrocytes, brain, liver and kidney; while

therapeutic use of 20 mg/kg melatonin results in significant reduction in the MDA levels in all compartments compared with control groups; their results are found compatible with those reported previously [15]. In this respect also, lead depletes the natural antioxidant molecule, the glutathione in the erythrocytes, brain, liver and kidney, and the use of melatonin prophylactically improves the levels of this antioxidant thiol in their compartments; their results are in agreement with those reported by others [16].

Lead exposure results in a significant accumulation of lead in all brain regions with maximal levels occurring in the hippocampus. It was also noted that changes in glutathione, lipid peroxidation products, intracellular calcium and membrane fluidity were consequences of lead toxicity. Neurotoxicity associated with lead exposure is believed to be the result of a series of perturbations in brain metabolism and, in particular, it is a consequence of oxidative stresses [17]. In present study melatonin reduced the severity of each change indicative of oxidative damage. Melatonin is a known direct radical scavenger and an indirect antioxidant with high efficacy in the brain [18]. Neuroprotective effects of melatonin have been demonstrated in many models of neuronal cell death in which oxygen free radicals are involved. In addition to its antioxidant effects, several other mechanisms may be involved in the neuroprotection mediated by melatonin; these include interactions with calmodulin and microtubular components, blockade of increases of intracellular Ca^{2+}, inhibition of activation of $NF\text{-}_KB$ by cytokines such as tumor necrosis factor α, inhibition of the expression of inducible nitric oxide synthase at the transcriptional level, changes in gene expression and activities of antioxidant enzymes and improved efficiency of mitochondrial oxidative phosphorylation[19].

Significant decrease in both Hb and PCV were found in the animals groups challenged with lead compared with control groups, while prophylactic use of melatonin showed significant improvement in these parameters compared with positive control groups, and these results are compatible with those reported by others [20]. After absorption of lead into the blood, 99% of lead is bound to erythrocytes and the remaining 1% stay in plasma to be carried to other tissues.

Decreased hematocrit and hemoglobin levels might arise from reduction in serum copper as well as reduced iron metabolism and consumption induced by lead [20]. Development of anemia in lead toxicity may be attributed to the decreased red blood cell survival because of the increased membrane fragility, reduced RBC count, decreased hemoglobin production, or summation of all these factors [21]. A previous study showed that melatonin prevents Pb-induced loss of Fe, Cu, and Zn from liver, and protected both ALAD and ferrochelatase enzymes in lead-intoxicated rats; thus enhancing heme biosynthesis and increasing hemoglobin content accordingly. Therefore it was suggested that melatonin preserves the availability of cellular antioxidants and eliminates free

radicals as evidenced by decreasing lipid peroxidation [22], the finding where the present study agreed with serum enzymes AST, ALT, and ALP showed significant elevation in rats exposed to lead, administration of melatonin reduces these activities but remain significantly elevated compared with control groups, these findings are compatible with other previous studies [22,23]. Increasing the activities of AST, ALT and ALP in serum was most likely a consequence of the hepatotoxic effect of lead, the accumulated lead in the liver directly damaging the hepatocytes, primarily by destroying the permeability of the cell membrane, which results in the increased release of cytosolic enzymes AST, ALT and ALP into the circulation. administration of melatonin produces a significant reduction in liver enzymes activity in serum; it is a potent free-radical scavenger, an effect which protects plasma membrane damage and preserve integrity of the homeostatic mechanisms that regulate intracellular contents of ions, proteins and other molecules; this is thought to be mostly attributed to hydroxyl and peroxyl radicals scavenging properties of melatonin [24].

The finding of the present study as regard to the increase in creatinine and urea concentrations in rats intoxicated with lead is in agreement with previous reports [24,25]. However, such increase may indicate impairment in kidney function. About 50% of kidney function must be lost before a rise in the serum concentration of creatinine can be detected. Therefore, urea and creatinine could be considered as suitable prognostic indicators of renal dysfunction in case of lead exposure. Antioxidant action of melatonin in the present study might play a role in the treatment of lead poisoning, and this is compatable with that reported by others [24,26].

The results of the present study enables the conclusion that melatonin, attenuates and reverses the tissue damage induced in experimental animals by lead acetate, and the prophylactic use of this pleiotropic hormone reveal a dose-effect relationship that support the idea of the oxidative stress-induced damage due to lead toxicity.

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