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Research Article **Zoology**

L-Carnitine ameliorates Cisplatin-induced testicular toxicity in rats

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KEY WORDS

Cisplatin,L-carnitin,Testis, Gonadotoxicity, Sperms.

ABSTRACT

Aim: To evaluate the effect of cisplatin on testes of male rats and to evaluate the possible curative effect of L- carnitine as an antioxidant. Methods: 18 male Albino Wistar rats were equally divided into three groups. Group I: control; Group II: cisplatin (7.5 mg/kg) for a single intraperitoneal (IP) injection; Group III cisplatin + 250 mg/kg/day of L-carnitine. Administration of L-carnitine by oral gavage started one day after cisplatin injection and was continued for 14 consecutive days. The rats were euthanized and the left testes were fixed in formaldehyde fixative for histopathological examination and morphometric analysis. The right testes were kept for biochemical tests to evaluate the levels of malondialdahyde (MDA) and reduced glutathione (GSH). Results: Cisplatin-induced impairment of spermatogenesis leading to a decreased in the testicular and gonadal organs weight, a decline in the sperms number, an increase in MDA level and a decrease in GSH level. Histological damage like degeneration, necrosis, arrest of spermatogenesis, congestion, and a decrease in the diameter of the seminiferous tubules were also observed. The rats that received cisplatin and L- carnitine showed non-significant changes in the testicular and gonadal organ weight comparing with the control rats and restored the control level of MDA and GSH. L-carnitine ameliorates the histological changes caused by cisplatin. Seminiferous tubules showed as normal with a non-significant change in their diameter. Conclusion: The findings of this study suggest that cisplatin induced testicular toxicity and L- carnitin could ameliorate this toxicity.

Introduction

Cancer is one of the leading reasons of death, and thus, the scientists have great efforts to improve cancer management [1]. Cancer treatments methods have been practiced in the past and many innovative methods, such as targeted therapy and chemotherapeutic drug were used. Chemotherapeutic drugs hinder the growth of tumors and even destroy the cancer cells. These drugs are generally considered as an effective method of treatment of cancer; however it can cause severe side effects as they can destroy either healthy cells or tissues [2].

Cisplatin (cis-diamminedichloroplatinum-II) is platinum based alkylating chemotherapeutic drug [3]. Cisplatin induces cytotoxicity in healthy tissues by production of reactive oxygen species, inducing mitochondrial oxidative damage and apoptosis, inhibiting antioxidant enzymes and releasing free radicals such as superoxide anions and hydroxyl radicals [4-5]. Cisplatin directly affects the spermatogonia and inhibits spermatogenesis leads to permanent infertility [4- 8]

L-carnitine (LC), a vitamin substance and small water soluble [6]. L-Carnitine is an antioxidant that plays a preventive role in the accumulation of lipid peroxidation end-products [7]. L-Carnitine plays a preventive role in reactive oxygen species (ROS) formation. So it is used in different pathological conditions associated with increased oxidative stress to ameliorate the oxidative damage [8].

Materials and Methods

Materials

Cisplatin was purchased from (MYLAN S.A.S., France). L- carnitine was purchased from (Sigma, C0283- 5G, USA).

Animals and Experimental design

Eighteen adult male Wistar albino rats weighing 200- 250 g were obtained from the Laboratory Animal Breeding and Experimental Research of Egyptian Drug Authority (EDA), Giza, Egypt. The animals were housed under standard laboratory conditions (12 hr light/dark cycle, 20±2°C, relative humidity 50±15%) for three days. Standard food pellets and tap water were available ad libitum. The experimental protocol was approved by the Ethical Committee of NODCAR.

The rats were randomly divided into three different experimental groups:

Group I (Control) received single intra-peritoneal (IP) injection of saline + daily oral gavages of 1mL of saline.

Group II (cisplatin) received a single IP injection of cisplatin at a dose of 7.5 mg/kg plus daily oral gavages of 1ml saline [3]

Group III (Cisplatin+ L- carnitine) received a single IP injection of cisplatin plus 250 mg/kg/day of L- carnitine by oral gavages [9].

Administration of L-carnitine started one day after injection of cisplatin and was continued for 14 consecutive days [10]

Testicular and gonadal organs weight

The rats were sacrificed after being anesthetized with diethyl ether. Rats were weighed in regularly, and their gonadal organs were dissected out and weighed. Each testis was then washed with normal saline to separate the

surrounding fat and connective tissues. After drying the surface with filter paper, the weights of the testis were recorded. Right testes tissues were frozen at -80°C for biochemical investigation. The left testes were removed for histological and morphometric investigations.

Sperms count

The sperm suspension was obtained by cutting the left caudal epididymis of a testis in few drops of saline and incubated at 37◦C for 30 minutes to allow sperms to leave the epididymal tubules. 20 µl of the sperm suspension were spread on a Neubauer hemocytometer and the heads were counted manually under a light microscope. Data were expressed as total number of sperm/ml [11-12].

Biochemical investigation

Right testes were homogenized separately in ice- cold Tris-KCl buffer (150mmol/l). The w/v ratio of the tissue to the homogenization buffer was (1:10 w/v). Aliquots were prepared and used for determination of different biochemical markers.

Supernatants were collected and assay for lipid per-oxidation (MDA) was performed. Determination of MDA in testicular homogenate is based on its reaction with thiobarbituric acid (TBA) to form a pink complex with an absorption maximum at 535 nm. The concentration of reduced glutathione (GSH) was estimated according to Sedlak and Lindsay (1968). GSH level was measured by the reaction of 5, 5´- dithiobis-2-nitrobenzoic acid (DTNP) with GSH at pH 8.2 and was expressed as nmol/g tissue.

Histological and Histomorphometric Investigations

For histological studies, animals were dissected and their left testes were removed and fixed in 10% neutral formalin for 24 hours, washed in running tap water for 24 hours and transferred to 70% ethyl alcohol. Tissues were dehydrated in ascending series of ethyl alcohol, cleared in xylene and embedded in wax. Sections of 5 µm thicknesses were cut using rotary microtome and mounted on clean slides without using any adhesive medium. Sections were stained with Ehrlich's haematoxylin, counterstained with eosin and photographed. Histological analysis was performed using a light microscope (Leica DM 4000, Germany). Seminiferous tubule diameters were measured using the same microscope and a computer-supported by image analysis program Image J version 1.48). Histomorphometric measurements of seminiferous tubule (diameter of seminiferous tubule) were performed in 10 randomly selected areas in six cross-sections for each Group, and the results were compared to the control group.

Statistical analysis

The data were subjected to statistical analysis by using Graph Pad Prism 5 statistical analysis program. The test type was Dunnett's multiple comparison test ($P < 0.05$) which accepted as significant [13-14].

Results

The relative testicular and gonadalorgans weight and sperms count

The testicular and gonadal organs weight were significantly ($P < 0.05$) decreased in cisplatin treated rats compared with

control group. Rats that post-treated with 250 mg/kg of L-carnitine showed a significant (P≤ 0.05) decrease in these parameters as compared to the control rats while showed a non-significant (p ≥ 0.05) change when compared with cisplatin injected rats (Figure1).

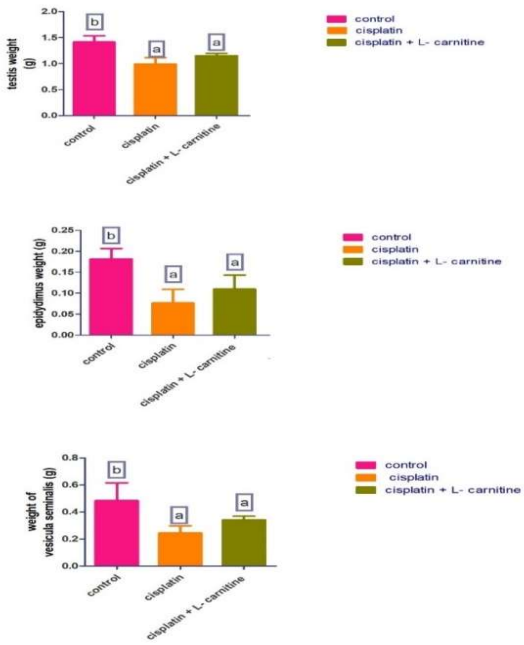

Fig (1): Effect of cisplatin and post-treatment of L-carnitine on the testicular and male gonadal organs weights in rats. Data are represented as mean ± SD, (n=6) P ≤ 0.05.

sperms count

Sperms counts were significantly (P < 0.05) decreased in cisplatin treated rats compared with control group. The rats that post-treated with 250 mg/kg of L-carnitine showed a significant (P ≤ 0.05) increase in sperms counts as compared to the cisplatin group while showed a non-significant (p ≥ 0.05) change when compared with control group (Figure 2).

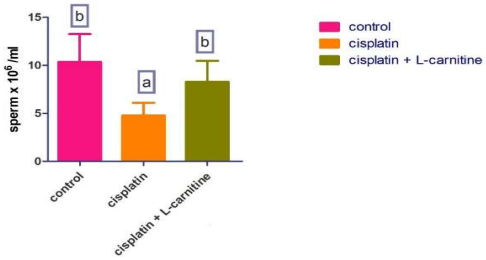

Fig (2): Effect of cisplatin and post-treatment of L- carnitine on sperms counts. Data are represented as mean ± SD, (n=6). P≤0.05.

Biochemical investigation

MDA level as indicators of oxidative stress in testes are presented in Figure 3. The data showed that the testicular of MDA level in cisplatin treated rats showed a significant increase (P ≤ 0.05) when compared with the control group. Treatment with L- carnitine showed a non-significant increase (p ≥ 0.05) in the testicular MDA when compared with the control group but showed a significant decrease (P ≤ 0.05) when compared with the cisplatin group.

GSH level as antioxidants showed a significant decrease (P ≤ 0.05) in the GSH content in cisplatin treated rats when compared with the control group. However, the rats that treated with L-carnitine showed a significant decrease (P ≤ 0.05) in the GSH content when compared to control group and showed non-significant increase (P ≥ 0.05) when compared with the cisplatin group, respectively (Figure 3).

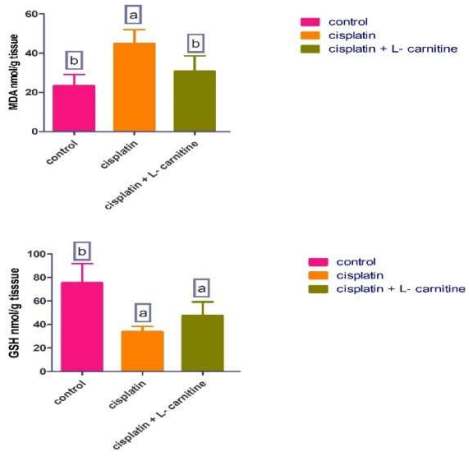

Fig (3): Effect of cisplatin, and post-treatment of L- carnitine on (MDA) and (GSH). Data are represented as mean ± SD, (n=6), P ≤ 0.05.

Histological results

The testis of cisplatin treated rats showed several pathological alterations where severe deformed and atrophied seminiferous tubules with spermatogenic arrest that detached from the basement membrane were observed. Leydig cells were atrophied with pyknotic nuclei. Spermatogenic cells showed cytoplasmic vacuolization with many multinucleated giant cells were also observed. The testis of spermatogenic arrest and improved of leydig cells architecture (Figure 4). cisplatin and L- carnitin post-treatment group showed normal seminiferous tubules with few seminiferous tubules that display irregularities in their outlines which were occasionally seen. It also showed mild

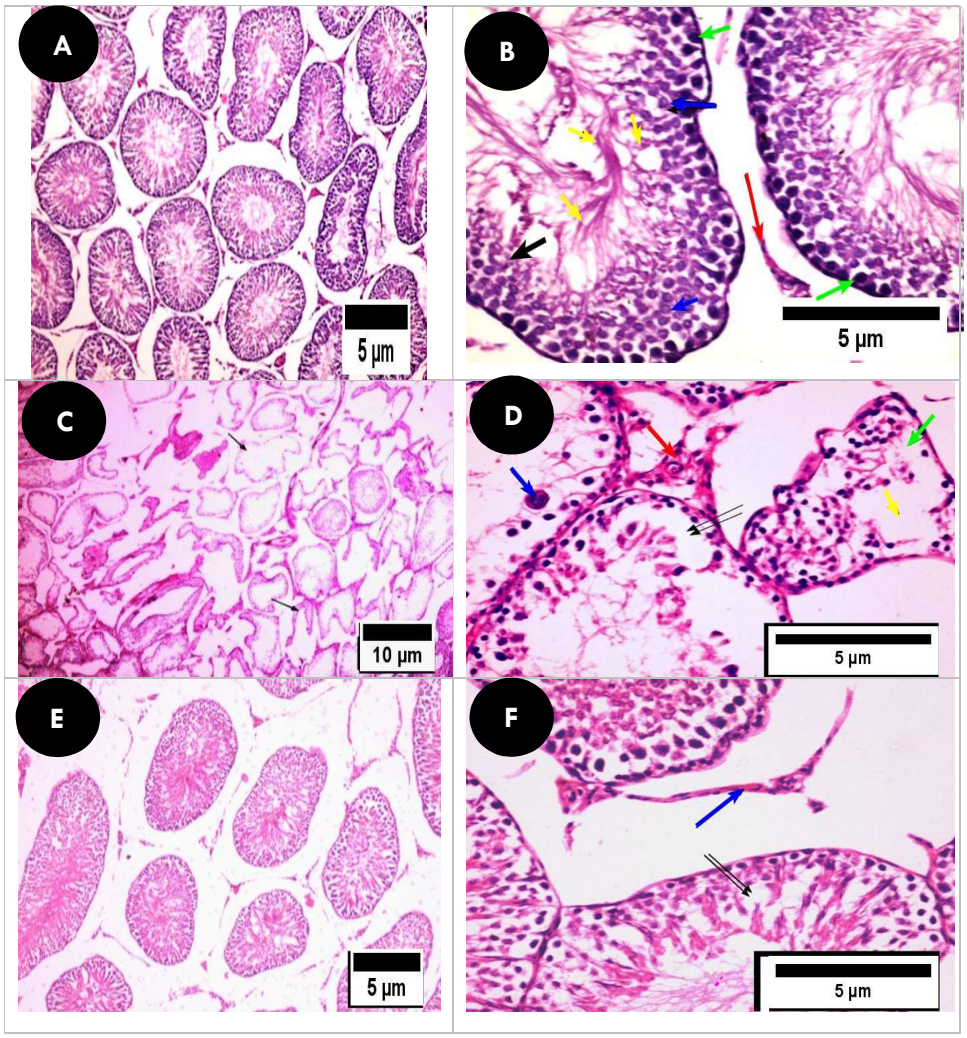

Fig (4): A-B Hematoxylin and eosin stained sections of control group showing: A- photomicrograph of the transverse section of the testis of the control rats showing seminiferous tubules. B- High magnification of Fig. A showing seminiferous tubules and interstitial leydig cells (red arrow). Note the presence of normal spermatogenic lineage epithelium; spermatogonium (green arrows), spermatocyte (blue arrows) and spermatids (black arrow), spermatozoa (yellow arrows). C photomicrograph of seminiferous tubules of cisplatin treated rat showing severe atrophy in seminiferous tubules with spermatogenic arrest (black arrows). D- High magnification of Fig. C showing seminiferous tubule showing spermatogenic arrest and detachment (black arrows), extensively atrophied tubule (yellow arrow), cytoplasmic vacuolization and Pyknotic leydig cells (red arrow). E-photomicrograph of seminiferous tubules of Cisplatin + L- carnitin adult rat showing normal seminiferous tubules with leydig cells in between it. F- High magnification of Fig. E showing seminiferous tubule with mild spermatogenic arrest (black arrows) and improved of leydig cells architecture (blue arrow). (H&E)

The data showed that the diameter of the seminiferous tubules were significantly ($P < 0.05$) decreased in cisplatin treated rats compared with the control group. The rats that treated with cisplatin and L-carnitin showed a significant ($P < 0.05$) decrease in the previous parameter as compared to the control rats while showed a non-significant ($p \geq 0.05$) change as compared to cisplatin group, respectively (Figure 5).

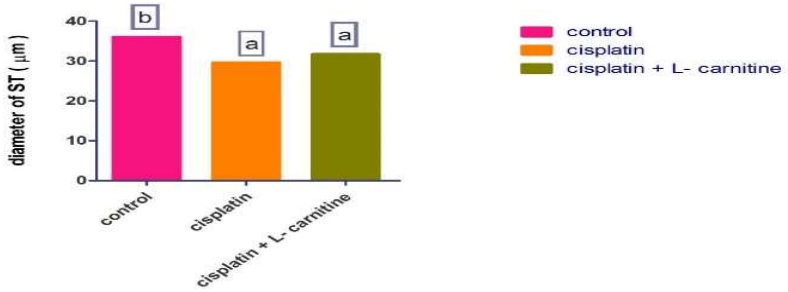

Fig (5): Effect of cisplatin and post-treatment of L- carnitine on the diameter of the seminiferous tubule Data are represented as mean ± SD, (n=6), P ≤ 0.05.

Discussion

Chemotherapeutic treatment may result in a short-term or long-term gonadal damage resulting in subfertility or infertility. Chemotherapeutics kill or destroy the body cells by two main ways: one is to upset the normal DNA synthesis of dividing cells undergoing meiosis and mitosis by their metabolites; another is to generate ROS that induce apoptosis or death of the cells [15]. Cisplatin toxicity leads to reproductive damage and hence male sterility by increasing the production of ROS. ROS might reduce the capabilities of the cell by DNA injury [16].

The current work was done to show the possible ameliorative effect of L– carnitine to face cisplatin-induced testicular toxicity in rats. The present data showed that there was a significant decrease in the testicular and gonadal organs weight after cisplatin injection. Previous studies reported that cisplatin has a harmful effect on the testis and its gonadotoxicity was evident by gonadal organs weight loss and reduced [20-21].

Longchar and Prasad (2015) [19] reported that the acute exposure to antineoplastic agents like cisplatin has shown an increase in the rate of germ-cell apoptosis in the experimental animals. It can also lead to

decrease reproductive organ weights, azoospermia and degenerated spermatogenic cell.

In the current study, markers for oxidative stress in the testicular tissue were evaluated and we found that cisplatin administration caused a significant increase in MDA with a remarkable reduction in GSH. GSH is a non-enzymatic antioxidant, shares mainly in scavenging hydroxyl radicals and singlet oxygen directly during oxidative stress.

The present finding was consistent with other studies, which reported that cisplatin exposure induced disruption of the antioxidant system and ROS overproduction and this lead to reduction of cellular antioxidant defenses like reduced GSH in addition to increased lipid peroxidation and its product MDA. Exposure to cisplatin can disturb redox balance, which is indicative of the oxidative type of the stress leading to the biochemical, physiological and histological disorders [20].

Salem et al. (2012) [21] agreed with this current paper and reported that ROS generated during normal cellular processes are immediately detoxified by endogenous antioxidants like GSH, etc., but excessive ROS accumulation by cisplatin causes an antioxidant status imbalance leading to lipid peroxidation and GSH reduction. Increased reactive oxygen species that attack cell membrane lipids lead to the increase in lipid peroxidation which leads to the increase in the testicular tissue levels of MDA, a by-product of lipid peroxidation that considered the best index of oxidative stress. However, GSH that considers a strong anti-enzymatic antioxidant that has a protective role in injury against oxidative stress, moderates cellular damage that is related to the increase of ROS and modulates apoptosis.

The histopathological examination of the present study explained the reduction in testis weight by reporting a moderate to severe gonadal atrophy with germ cells degeneration in the seminiferous tubules and spermatogenic arrest (reduction in spermatogenesis). Moreover, thickness of the seminiferous tubule and diameter of seminiferous tubules decreased in cisplatin group while they were increased in the animals that were treated with L- carnitine compared to cisplatin group. Al-Shahari et al. (2021) [22] agreed with the present findings and they approved that there is a positive relation between the tubular diameter and the spermatogenic activity.

Spermatogenesis can be severely influenced by drugs used in chemotherapy. Doxorubicin is an anticancer compound widely used for its anti- proliferative properties induce cell cycle arrest and cell death in replicating somatic cells. The high levels of DNA synthesis and cellular proliferation in the male germ cells may also play a role in the susceptibility of spermatozoa to damage by free radicals [23].

Cisplatin triggers cellular responses involving multiple pathways, including DNA repair, transcription inhibition, cell cycle arrest, cellular transport system impairment, ATPase activity reduction and mitochondrial damage, apoptosis, necrosis, oxidative stress, fibrogenesis, inflammation, hypoxia and mitochondrial damage. It also induces cytotoxic effects in healthy cells [3].

In this study, administration of L-carnitine alleviated the reduction in germ cell numbers, repaired the morphological damage in testicular tissues and exhibited ameliorative effects against the damage caused by cisplatin. Numerous studies agreed with our findings [25-28].

L-carnitine, a vitamin substance occurring naturally, also known as vitamin BT, plays an important role in energy metabolism of the human body. L-carnitine could eliminate free radicals, protecting sperm cells from oxidative damage [15]. L-carnitine is an endogenous substance that is commonly present in male genital organs [25]. L-carnitine has antioxidative, antiperoxidative, and free radical scavenging properties which protect the cellular DNA and membranes against cellular damage induced by free oxygen radicals. L-carnitine protects the germ cells from oxidative stress by preventing the formation of ROS produced by the xanthine/ xanthine oxidase system and decreases damage to the cell membrane [26]. L-carnitine can facilitate β-oxidation of long-chain fatty acids, participate in branched chain amino acids metabolism and stabilize cellular membranes. Moreover, it can increase antioxidant enzymes activities. Furthermore, L-carnitine could improve antioxidant status and free radicals detoxification and provide strong antigenotoxic effect in Cisplatin intoxicated rats [27].

The use of antioxidants is useful in reducing the adverse effects of drugs and is an important strategy in protecting the male fertility during the course of chemotherapy [22]. To reduce side effects of the drug, usage of antioxidant compounds may be beneficial and important strategy for protecting of male fertility along chemotherapy period.

Conclusion

The results proved that L- carnitine as an antioxidant could ameliorate the toxicity induced by cisplatin on both biochemical and pathological levels in the testicular tissues.66, no. 3, pp. 419–429, 2014.

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التأثير المعالج لل ال-كارنيتين على خصية الفئران الذكور المعالجة ب السيسبلاتين

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2. قسم دراسة الانسجة - هيئة الدواء المصرية

الغرض من هذه الدراسة هو التحقق في تأثير السيسبلاتين على خصية الفئران الذكور بيوكيميائيا ، ونسجيا حيث تم إيواء 18 فئران من ذكور ألبينو ويستار في ظروف معملية قياسية (12 ساعة من الضوء/ دورة الظلام ، 20 ± 2 درجة مئوية ، الرطوبة النسبية 50 ± 15٪) لمدة أسبوعين حيث تم تقسيم الحيوانات إلى ثلاث مجموعات (ن = 6). المجموعة الأولى السيطرة ؛ المجموعة الثانية سيسبلاتين (7.5 مجم / كجم)، المجموعة الثالثة سيسبلاتين + 250 مجم / كجم / يوم من ال- كارنيتين. تم قتل الجرذان بطريقة القتل الرحيم بعد 14 يوم وتم الاحتفاظ بالخصيتين اليسرى لثلاثة حيوانات مثبتة في مثبت الفورمالديهايد لفحص الأنسجة المرضية. تمت إزالة الخصيتين اليمنى للحيوانات الثلاثة الأخرى للاختبارات البيوكيميائية وأظهرت النتائج أن تناول ال- كارنيتين كمضاد للأكسدة إلى تحسين وزن الجسم وعدد الحيوانات المنوية في تلف الخصية الناجم عن سيسبلاتين. كما أظهرت النتائج ان ال كارنيتين يسبب انخفاضاً معنوياً في مستويات الأكسجين التفاعلي مقارنة بمجموعة سيسبلاتين. كما أن ال كارنيتين يزيد من مستويات إنزيمات مضادات الأكسدة . كما أظهرت النتائج ان ال- كارنيتين يؤدى الى تحسنًا في التغيرات النسيجية المرضية الناتج عن تلف الخصية الناجم عن السيسبلاتين. كما أظهر تناول ال- كارنيتين زيادة في قطر الأنابيب المنوية في تلف الخصية الناجم عن سيسبلاتين.