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Valproate-Induced Testicular Histotoxicity in Adult Male Albino Rats and its Attenuation by L Cysteine

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Abstract

Background: Valproate (VPA) is used as an antiepileptic drug for the treatment of generalized and partial epilepsy and as a prophylaxis for the febrile convulsions of childhood.

Aim of Study: This study evaluated the protective effect of L cysteine on valproate-induced testicular abnormalities in male Wistar rats.

Material and Methods: A total of 30 rats were grouped into three groups, each having 10 animals. Sodium valproate (500mg/kg) was given intraperitoneally for 10 days alone in group II and in accompany with L cysteine (100mg/kg) was given orally in group III with additionally a control group given only saline. On day tenth, all animals were sacrificed and the different parameters were recorded.

Results: The histopathological examination revealed that valproate had caused degeneration and desquamation of germinal cells in the epithelium, edema and congestion. These degenerative changes were significantly improved by giving L cysteine. The apotosis and the oxidative stress were suggested by our study to be the causative mechanisms of Valproate testicular toxicity as proved by CASPASE-3 reaction and the GSH and MDA levels which were significantly improved by giving L cysteine as antioxidant.

Conclusion: This study supposed that VPA disturbs the testicular histology due to its toxicity by inducing oxidative stress, but the LC could improve these side effects.

Key Words: *Valproate – L cysteine – Testes – Rats.*

Introduction

VALPROATE (VPA) is used asacentral neurological drug for the management of the convulsions resulting from different types of epilepsy, especially the formsof absence, myoclonic, tonic-clonic, atonic, and mixed type seizures, and as aprotectionfor the febrile convulsions of childhood **[1,2]**.

Many previous studies mentioned testicular atrophy and histologically demonstrated spermatogenetic arrest in male rats as a side effect of the use of higher doses of valproate **[3]**.

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In spite of the use ofVPA for treatment of pediatric epilepsy, most studies on the effect of VPA on the genital and neuroendocrine systems have extensively made on adult male rats **[4]**.

Accordingly, more papers were done about the sexual effects of antiepileptic drugs (AEDs) on male reproductive system that showed sexual dysfunction, including reduced potency and hyposexuality in 38-71% of men with epilepsy **[5]**.

However, Røste et al., **[6]** declared the effects of the long-term use of AEDs by disturbing the sex hormones and reducing the sperm quality without correlation with specific drugs.

In another study done by Walker et al., **[7]**, there is an association of the testicular atrophy in both rats and dogs with long term use of valproate treatment. Moreover, Cansu et al., **[8]** added that chronic valproate treatment has also delayed the pubertal maturation by reducing the testicular growth and spermatogenesis in rats.

Many other mechanisms were supposed to resolve the toxicity of VPA on the testis; Wang et al., **[9]** described the molecular mechanism as a possible way of VPA toxicity on the testes explained by the localization of androgen receptor (AR) as a member of the nuclear receptor superfamilyon the testis and epididymis playing important roles in male spermatogenesis and fertility and Røste et al. **[6]** added another mechanism of the testicular VPA toxicity by increasing testosterone antecedents following VPA use causing decrease of the release of pituitary hormones via the negative feedback mechanism.

A possible potential mechanismproved by Zhang et al., **[10]** by findinga correlation between the histological and oxidative stress induced by VPA in the testis which is considered a major target organ for oxidative radicals due to its high content

of polyunsaturated lipids membrane. This way was confirmed by Hamza and El-Shenawy [11] who described the injurious effects of VPA on the testis weight and oxidative damage and also, Henriksenet al., [12] explained the reduction in testosterone levels by damaging the germ cells.

Accordingly, L cysteine (LC) was utilized as a potent antioxidant for the treatment of VPA testicular toxicity by its ability of scavenging reactive oxygen species (ROS) directly, and indirectly due to its reduced thiol moiety [13].

In other words, Pereira-Filho et al., [14] described the antioxidant role of LC in the protection of the testis against VPA toxicity bythe production of glutathione through hydrolysis into cysteine enhancing glutathione-S-transferase activity leading to its intracellular defense against oxidative stress and promotes detoxification.

Moreover, Ahmed et al., [15] enumerated that the protective mechanisms of this LC effect against VPA testicular toxicity may be due to the enhancement of the tissue anti-oxidant capacity which benefits the physicians in case of treatment with VPA testicular damage by the use of L cysteine (LC).

The aim of the present study:

Was to investigate VPA induced testicular damage and associated hormonal disturbances in adult male rats with the evaluation of the possible protective role of the antioxidant substances like LC in the correction of VPA induced testicular damage.

Material and Methods

Material:

Animals:

Thirty male Wistar rats (weighed from 195 to 230 grams) were put in plastic cages and fed orally at the same temperature (21-22 C) and humidity on a 12 hour light and darkness cycles at an air exchange rate of 18 changes per hour. Rats in all groups were given free access to food and water. The feeding and the drug administration were under the control of the vegetarians in the animal laboratory of the Faculty of Medicine, Cairo University during the duration from 20 July 2021 to 30 July 2021.

Chemicals:

VPA was obtained from (Sigma-Aldrich, Inc., USA) in the form of vials and L cysteine was obtained from pharma company in the form of capsules.

The rats were divided into three groups with 10 rats each:

Group I (the control group): Half of them were injected intraperitoneally (i.p.) with normal saline and the other half were given saline via gastric tube.

Group II (the VPA given group): Were injected with a single dose of VPA (Sigma-Aldrich, Inc., USA) at 500mg/kg BW per day for 10 consecutive days 16.

Group III (the VPA and LC given group): Were injected with a single dose of VPA) at 500mg/kg BW per day for 10 consecutive days and treated with L cysteine (LC) at a dose of 100mg/kg BW15 via gastric tube.

All animals were sacrificed by decapitation 4-6 hours after their last medication intake. Each testicle was weighed separately and immediately cut in two pieces. One half was formalin fixed in 4% buffered formaldehyde for morphological and immunohistochemical examination. The other half of the testis was immediately stored at –70ºC until further analysis.

Methods:

I- *Histological preparation:*

Testicular tissue sections were fixed in bouin solution and subsequently embedded in paraffin. 4-5gm thick sections were prepared for hematoxylin eosin (H&E) and Masson trichrome staining (Applichem GmbH, Darmstadt, Germany). Preparations were analyzed under a light microscope (DM6200; Leica Microsystems GmbH, Wetzlar, Germany). Photos were taken using the Olympus DP20 camera (Olympus Corporation, Tokyo, Japan).

1- *Biochemical analysis:*

A- Lipid peroxidation:

The LPO levels were measured according to the method described by Ohkawa et al., [17] using biodiagnostic kits. This method was based on estimation of the released malondialdehyde (MDA) molecules, as a result of oxidative damage of cell membranes. The concentrations of MDA were expressed as in nanomole of MDA per gram of tissue.

B- Bioassay of non-enzymatic antioxidants:

Non-enzymatic (glutathione, GSH) antioxidants were estimated in the homogenate of the kidneys of control male albino rats, those administered with repeated clinical doses of Gentamicin and those administered with repeated clinical doses of gentamicin and curcumin. The concentrations of

GSH in tissue homogenates were estimated and expressed in milligrams of GSH per gram of tissue **[18]**.

II- Immuno histochemistrigical preparation:

Testicular tissue blocks were fixed in 2.5% formaldehyde and were subsequently embedded in paraffin. 1-3Mm sections were prepared and immunologically stained for NF-κB/p65 (1:100, Anti NF-κB/p65 antibody, ab16502; Abcam, Cambridge, UK), caspase 3 (1:100, rabbit anti caspase 3 polyclonal antibody, ab4051; Abcam) and 8 OHdG (1:50, KOG HS10E, Dako Envision kit; Japan Institute for the Control of Aging (JaICA), Nikken SEIL Co., Ltd., Shizuoka, Japan), using the Ventana Benchmark GX (USA) device. Then the secondary antibody was applied (UltraView Universal DAB Detection kit, 760 500; Ventana Medical Systems, Inc., Tucson, AZ, USA). Sections were examined under a light microscope and photos were taken as described above.

III- Histomorphometric analysis:

Image analysis was performed using the software Leica Quin 500, Germany. The area percent of collagen fibers in Masson's trichrome stain and that of positive BAX as well as PCNA were measured in a standard measuring frame using a magnification x 400 by light microscopy transferred to the monitor's screen. These areas were masked by a green color using the computer system. Area percent values for each group were obtained from 5 different fields from different slides. Values were presented as a mean and standard deviation and statistically analyzed.

IV- Statistical analysis:

Data were analyzed using SPSS. All data are expressed as means ± standard deviation. Comparisons between groups were tested using ANOVA or Kruskal-Wallis variance analysis followed by Tukey's multiple comparison test or the Mann-Whitney U test. Statistical significance was set at $p<0.05$.

Results

Light microscopy results:

The histology of the testes of the rats of group Ishowed noabnormalities considering the typical histology of the connective tissue, vessels and Leydig cells with regular basal laminae (Fig. 1A). The Masson reaction was normal exhibiting normal collagen fibres (Fig. 2A).

The histological structure of testes of the rats of VPA given group showed oedema accompanying the destruction of the germinal epithelial cells of the seminiferous tubules. Spermatocytes were disconnected from spermatogonia characterized byatypical nuclei. Also, the spermatozoa and spermatids were reduced. There was degeneration of the basal laminae of the seminiferous tubules. Moreover, the interstitial spaces showed congestion and The Leydig cells decreased with fragmented nuclei (Fig. 1B). The Masson reaction exhibited increased collagen fibres and fibrosis (Fig. 2B, Table 1 and Histogram 1).

In the VPA and LC given group, the testes showed less vacuolization of inter epithelial cells of the seminiferous tubules than the VPA group with normal spermatogonia and spermatids. Spermatozoa in the seminiferous tubules were increased in number as compared to the VPA group. The interstitial space of the testes of the VPA group appeared less hyalinized with more regularity of the basal layer of the seminiferous tubules was less than the corresponding VPA group (Fig. 1C). The Masson reaction showed less collagen fibres and fibrosis than the VPA group (Fig. 2C, Table 1 and Histogram 1).

Immunohistochemical (IHC) results:

There was highly expressed reaction for caspase-3 in the cytoplasm of germinal cells of the testes of group II in comparison with the negative reaction expressed in the testes of group I. The expression of caspase-3 reaction in group III is less than that of group II (Fig. 3, Table 1 and Histogram 1).

Biochemical analysis:

The level of GSH was increased in the testes of group III in relation to group II while the level of MDA was decreased in the testes of group III in relation to those of group II (Table 1 and Histogram 1).

Statistical analysis:

With the exception of the controls, the weights of the testes of group III showed a significant decrease as compared with the testes of group II. The area percent of the collagen fibres of the testes of group III was significantly decreased as compared with those of group II. The optical density of the caspase-3 reaction of the testes of group II was significantly increased as compared with those of group III. The level of GSH in the testes of group III was significantly increased as compared with group II while the level of MDA in the testes of group III was significantly decreased as compared with group II (Table 1 and Histogram 1).

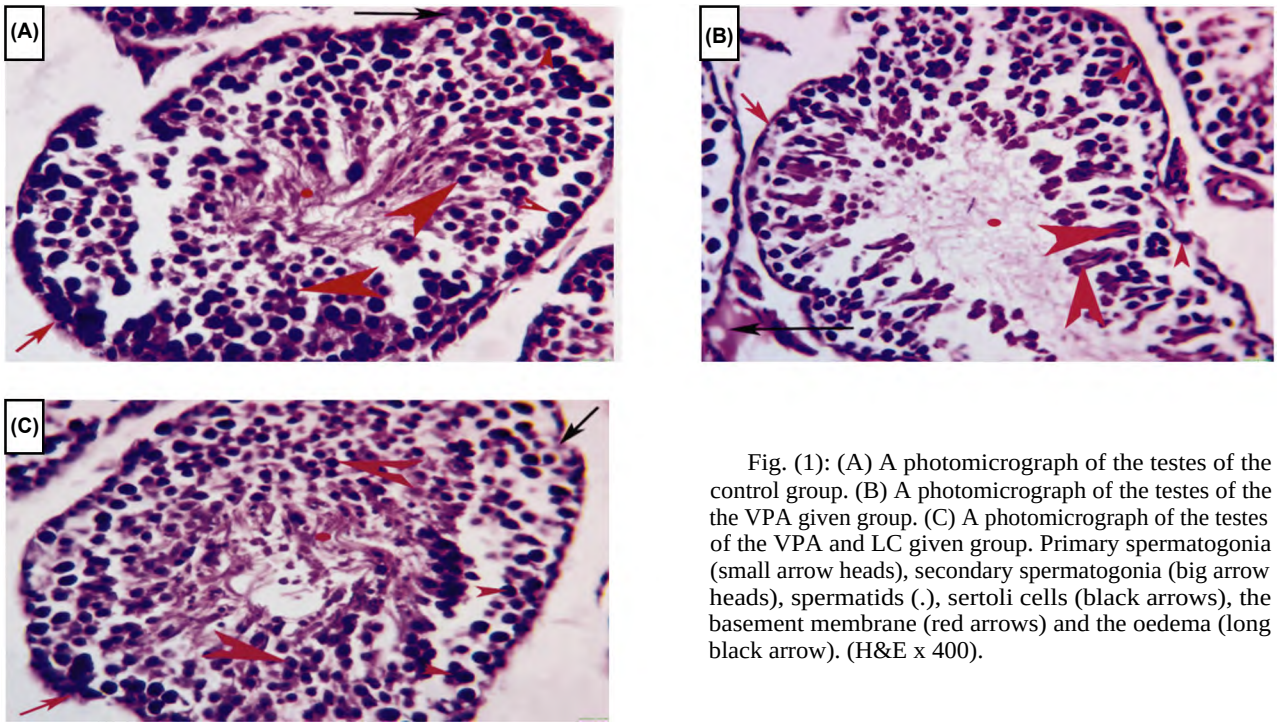


Fig. (1): (A) A photomicrograph of the testes of the control group. (B) A photomicrograph of the testes of the the VPA given group. (C) A photomicrograph of the testes of the VPA and LC given group. Primary spermatogonia (small arrow heads), secondary spermatogonia (big arrow heads), spermatids (.), sertoli cells (black arrows), the basement membrane (red arrows) and the oedema (long black arrow). (H&E x 400).

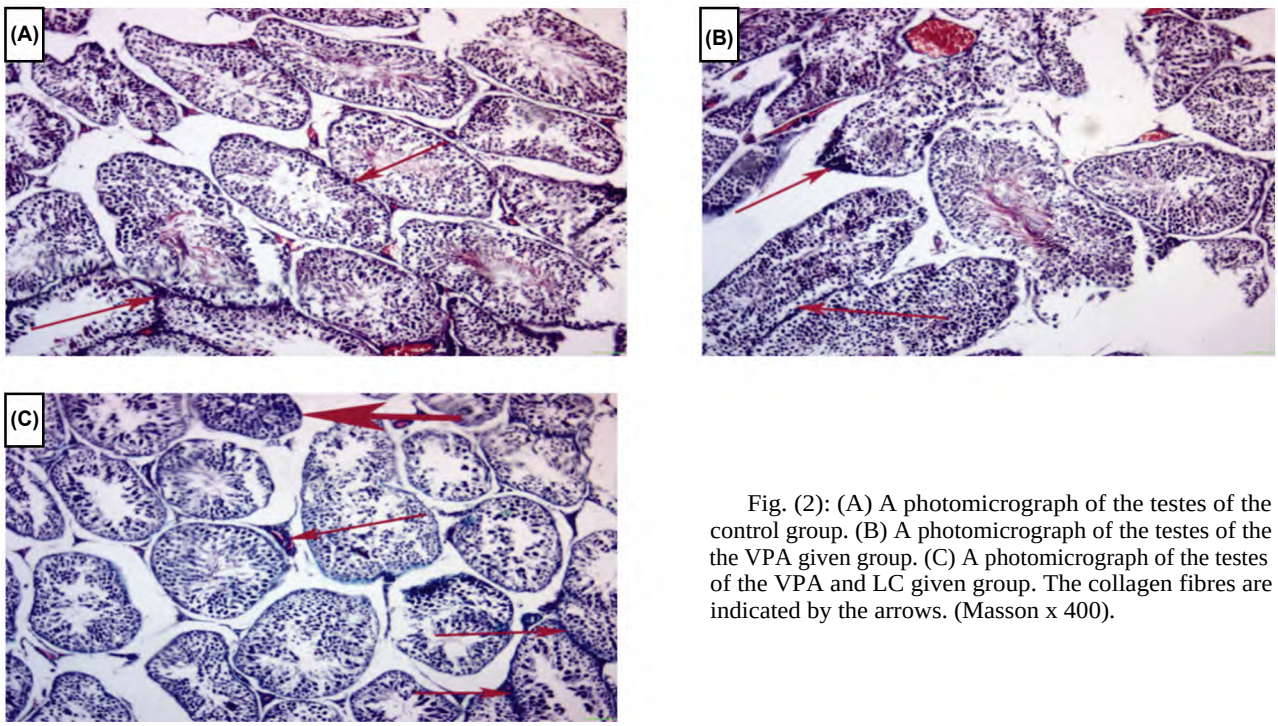


Fig. (2): (A) A photomicrograph of the testes of the control group. (B) A photomicrograph of the testes of the the VPA given group. (C) A photomicrograph of the testes of the VPA and LC given group. The collagen fibres are indicated by the arrows. (Masson x 400).

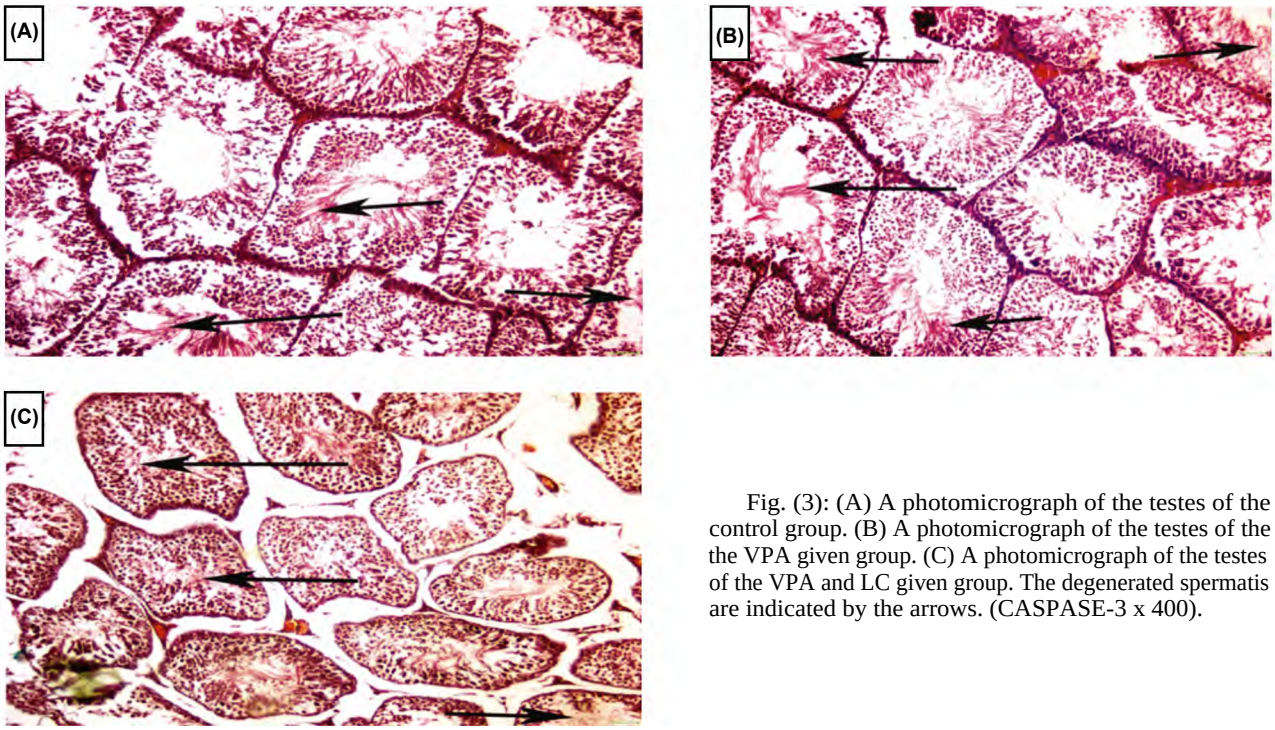
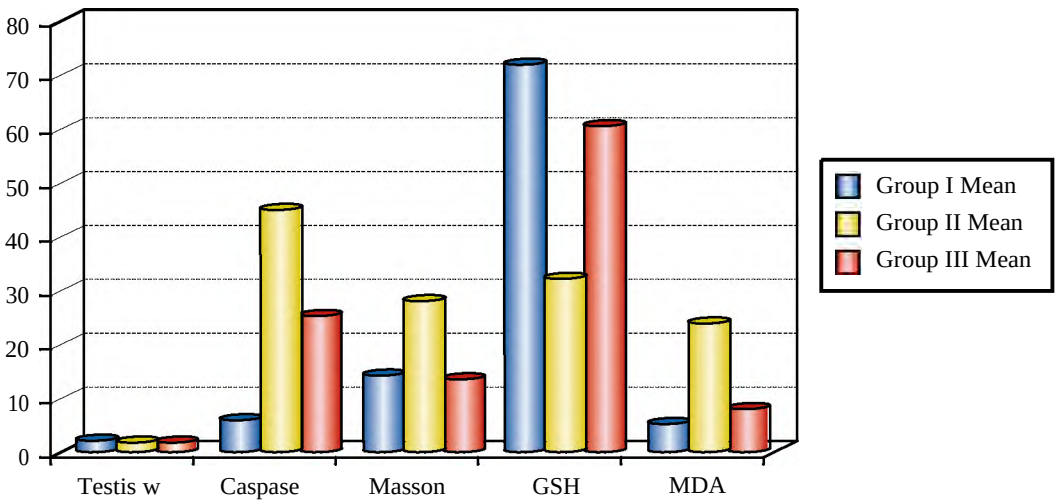


Fig. (3): (A) A photomicrograph of the testes of the control group. (B) A photomicrograph of the testes of the the VPA given group. (C) A photomicrograph of the testes of the VPA and LC given group. The degenerated spermatis are indicated by the arrows. (CASPASE-3 x 400).

Table (1): The relations between the different groups.

	Group I Mean ± SD	Group II Mean ± SD	Group III Mean ± SD
Testis w	2.024±0.082	1.713±0.057*	1.829±0.047*,**
Caspase	5.889±0.898	44.896±3.094*	25.193±2.605*,**
Masson	14.182± 1.236	27.997± 1.944*	13.599±0.796*,**
GSH	71.967±2.957	32.039±2.563*	60.507± 1.975*,**
MDA	5.130±0.636	24.012±3.050*	7.857±0.935*,**

* Statistically significant as compared to control group (group I).
** Statistically significant as compared to group II.



Histogram (1): The relations between the different groups.

Discussion

In the present study, we determined the toxicological effects of VPA on testis of rats depending on a single dose and duration. However, many studies were done to prove the toxicological effects of VPA on testis of rats to be dose and duration related including Nishimura et al., [19] who observed the VPA toxicity after 4, 7 and 10 days of 500mg/kg of VPA in the form of decreased testicular weight and spermatogenic abnormalities in the 10-day group in comparison toother groups at a 250mg/kg dosage.

Moreover, Roste et al., [20] described the testicular atrophy associated with Wistar rats when given 90-day treatment of 400mg/kg VPA, but not after 200mg/kg and Walker et al., [7] added that the testicular damage worsen with increasing the dose of VPA.

In our study, we found oedema accompanying the destruction of the germinal epithelial cells of the seminiferous tubules. Spermatocytes were disconnected from the basement membrane and spermatogonia characterized by atypical nuclei. Also, the spermatozoa and spermatids were reduced. There was degeneration of the basal laminae of the seminiferous tubules. Moreover, the interstitial spaces showed congestion and the Leydig cells decreased with fragmented nuclei and increased collagen fibres and fibrosis.

In spite of the different doses and durations used by Walker et al., [7], they reported similar toxicological damaging effects on the testes of the rats including reduced sperms, decreased testicular weights, and degeneration of the spermatogonia and increased fibrosis which gradually increased in severity according to the dose and the duration of VPA. In addition, Roste et al., [20] supported our study through detecting the testicular tubular atrophy, spermatogenetic arrest at the prophase of the first meiosis and decreased testicular weights in rats treated by VPA.

Moreover, Rätty et al., [21] used different anticonvulsive drugs for a period of 3 months in male rats and had reported reduced sperm countin the VPA treated rats associated with increased infertility.

In our trial to explain the toxicological effects of VPA on the testes of the rats, we measured the levels of GSH and MDA in the testicular tissues and found that the level of GSH was increased in the testes of group III in relation to group II while the level of MDA was decreased in the testes of group III in relation to those of group II. Depending on these results, the oxidative stress played an important role in the testicular pathological effects of VPA.

Our data were in agreement with the data presented by Zhang et al., [10] that documented increased the level of MDA in the neutrophils of VPA treated patients with inhibited activities of SOD. And CAT than the control groups.

Moreover, Vidya and Subramanian [22] observed the rise of MDA and hydroperioxides in the tissues of the VPA treated rats with a reduction in the level of GSH. These data were also supported by Sobanlek et al., [23] who detected insignificant increase in the level of MDA in the pediatric erythrocytes treated by VPA with insignificant depression in the level of GSH.

However, D'Souza et al., [24] supposed another mechanism for VPA testicular toxicity through the damage to Sertoli cells resulting indisturbances of intergerminal bridge and the formation of multinucleated giant cells (also called symplasts) via fusion of destroyed spermatids.

In our trial, we suggested the apoptosis as another mechanism for VPA testicular toxicity by detecting an increase in the caspase 3 reaction in group II with some moderate improvement in group III. These results were also observed by Cansu [25] who enumerated VPA apoptosis-inducing effect on human and rat granulosa cells by increasing caspase-3 activity. Further, Bairy et al., [4] reported VPA-induced testicular necrosis in addition to the congestion and oedema.

In contrary, Narayana et al., [26] mentioned cytotoxicity as a way of VPA testicular histopathological damages resulting inepithelial sloughing, atrophic changes and reduction in the germ cell numbers. In addition, Girish et al., [27] reported many histopathological effects with using VPA on the testes as congestion, interstitial edema and degenerative alternations in addition to thetheapotosis which was seen by Bairy et al., [4].

Finally, Tamber and Mountz [28] had mentioned many mechanisms for VPA cellular toxicity includingfree oxygen radical formation and lipid peroxidation, causing disruption of the structure and function of testis.

The LC has antioxidant characters because of its ability to go through the redox reactions directly or through the formation of Cysteine which can be formed in the human body under normal phys-

iological conditions if there was enough quantity of methionine whose its tripeptide GSH gave it the anti-oxidant properties **[29]**. Therefore, one of the important aims of the current research was to focus on the role of LC in reducing the testicular oxidative stress in case of treatment with VPA through inducing an increase of the GSH content of the cell.

El-Shenawy and Hamza, **[30]** demonstrated that LC -anti-oxidant activityplays an important role in protecting liver, kidney and brain tissues against the oxidative stress and Droge **[31]** showed that LC treatment declined the oxidative stress on the testes asproved by our conclusion.

Our data presented were compatible with the data presented by Zhang et al., **[10]** who measured higher levels of the MDA levels in neutrophils of VPA-treated patients with decreased activities of SOD and CAT than the control groups and supposed that the oxidative stress was the cause of the testicular damage induced in rats by VPA and subsequently, the use of the LC could improve the VPA testicular toxicity. Moreover, Girish et al., **[27]** and Bairy et al., **[4]** described an improvement of the histo-architecture of the testis and a decline of Johnsen's scores when using LC treatment with VPA. Inconclusion, this study supposed that VPA disturbs the testicular histology due to its toxicity by inducing oxidative stress, but the LC could improve these side effects. The histo-architecture of testis was also restored by the LC confirming its protective effect. The mechanism of the protective action of the LC because of its antioxidant property, which needs further research. Therefore, LC may be useful in epileptic patients on long-term VPA treatment if proved effective in clinical trials.

Conflict of interest: The authors of this article have no conflicts of interest.

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دراسة التغيرات الهستولوچية الناتجة عن عقار الفالبروات على خصية الفأر الأبيض البالغ ودور الإل سيستين فى تقليله

تعتبر مادة الفالبروات من الأدوية الهامة التى تستخدم فى علاج العديد من الأمراض العصبية. وقد تم إكتشاف أن استخدام الفالبروات يسبب تلف وإلتهاب أنسجة الخصية مما قد يؤدى فى النهاية لتليفها. وقد تم تسجيل عدة دراسات تجريبية لتقليل هذه الأعراض الجانبية باستخدام مركبات أخرى مع الفالبروات.

ويهدف هذا البحث إلى دراسة التأثير الضار للفالبروات على الخصية والدور الوقائى المحتمل لال سيستين. وقد تم إجراء هذه الدراسة على ثلاثون من الفئران البيضاء الذكور التى يتم تقسيمها إلى ثلاث مجموعات:

– المجموعة الأولى (المجموعة الضابطة)

– المجموعة الثانية:

وهى التى تم حقنها بعقار الفالبروات.

– المجموعة الثالثة:

التى تم حقنها بعقار الفالبروات مع ال سيستين.

وقد تم ذبح الفئران فى كل المجموعات طبقاً للفترات الزمنية الموضحة أمام كل مجموعة وتم تشريح الخصية وفحصها، وقد تم تجهيز شرائح مجهرية من الخصية وصبغها بالهيماتو كسلين والأيوسين وفحصها باستخدام المجهر الضوئى. كذلك تم صبغها بصبغة الماسون ثلاثية اللون بهدف فحص وتحديد كمية التليف بواسطة نظام الكمبيوتر المحلل للصور. بالإضافة إلى ذلك فقد تم تجهيز شرائح لفحصها لتحديد كمية التحلل التلقائى عن طريق الكاسباس-٣.

وقد أوضحت دراسة خصية الفئران التى تلقت الفالبروات بالمقارنة بالخصية فى المجموعة الضابطة تلفا فى التركيب الهستولوچى لها مع زيادة الالتهابات فى أنسجتها وتفكك فى الخلايا المئوية الأولية وتحلل فى الطبقة القاعدية زيادة نسبة التليف والتحلل التلقائى.

وقد لوحظ أن إعطاء ال سيستى مع الفالبروات قد أدى إلى تخفيض ملحوظ فى التغييرات السابق ذكرها فى الفئران التى تلقت الفالبروات فقط. ومع ذلك كان هذا الدور الوقائى لال سيستين فى الفئران التى تنتمى لنفس المجموعة التجريبية متباين، ففى معظم العينات كانت التأثيرات الضارة للفالبروات خفيفة مع الإحتفاظ بوجه عام بالشكل الطبيعى للخصية.

وفى ضوء نتائج هذه الدراسة فقد أمكن القول أن لعقار الفالبروات تأثيرات ضارة على الخصية فى الفأر الأبيض وأن إعطاء ال سيستين مع الفالبروات يمكن أن يقلل من تلك التأثيرات الضارة بشكل ملحوظ.

وهذه النتائج أدت إلى تطبيقات هامة فى الإنسان حيث ينصح بإعطاء الأفراد الذين يتعرضون للفالبروات ال سيستين للحد من تأثيرها الضار على الخصية.