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Studying the Protective Effect of N-acetyl cysteine and L-carnitine on Testicular Toxicity Induced by Valproic Acid Administration in Adult Male Albino Rats

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Abstract

Introduction: Sodium valproate (VPA) is a well-known antiepileptic drug used in treatment of generalized seizures and cause many toxic effects. **Aim**: This study aimed to highlight the VPA effects on testes in adult male albino rats and protective effect of N- acetyl cysteine (NAC) and L-carnitine. **Methodology**: Sixty adult male albino rats divided into six groups randomly, 10 rats each, group I: negative control group not received any treatment. group II: positive control group received NAC 150 mg/kg/day orally, group III: positive control group received L-carnitine 500 mg/kg/day orally, group IV: received VPA 400 mg/kg/day orally which equals 40/67 of Ld50 of valproic acid in rats, group V: received VPA 400 mg/kg and NAC 150 mg/kg daily orally, group VI: received VPA 400 mg/kg and L-carnitine 500 mg/kg daily orally for 45 days. **Results**: This study revealed high significant difference between group received VPA (IV) in form of marked decrease in serum testosterone compared to control groups (I, II, III), laboratory parameters are co-incident with histopathological findings in testes of these groups. We found a significant improvement in laboratory parameters in the form of higher serum testosterone levels in groups received antioxidants with VPA (V, VI), co-incident with histopathological findings in testes of these groups, with a higher protective power of L-carnitine than N- acetyl cysteine. **Conclusion:** Sodium valproate induces testicular toxicity in high doses (400 mg/kg) in male albino rats. There is a protective role for both NAC and L-carnitine. L-carnitine exhibited more protective effect than NAC on their administration with VPA.

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Key words Valproic acid, Sodium valproate, VPA, N-acetyl cysteine, L-carnitine, Testes

Introduction

Sodium valproate or valproic acid (VPA) is a well-known antiepileptic drug used in the treatment of many forms of generalized seizures and psychiatric problems to control epilepsy and regulate the mania associated with bipolar disorder (Lahneche et al., 2017). Many toxic effects are known about VPA such as thrombocytopenia, platelet aggregation, hepatotoxicity and pancreatitis (Shaalan et al., 2015).

VPA diminishes male fertile reproductive quantifications and hormonal levels in human and animals. VPA-administration causes atrophy of the testicles, seminal vesicles, epididymis and prostate (Iamsaard et al., 2017). Testicular damage has been linked with adverse reproductive problems and diminution of sexual hormone levels (Bairy et al., 2010).

Researches detected that VPA increase acrosomal reactions of precocious sperm and causes fibrosis of tunica albuginea in the testes of rats (Sukhorum and Iamsaard, 2017). The mechanism by which VPA toxicity leads to impaired sperm motility is not fully detected. Oxidative stress is thought to be responsible for VPA toxicity (Hamza and Amin, 2007).

N-acetylcysteine (NAC) is a precursor of amino acid L-cysteine and consequently the antioxidant glutathione (GSH), NAC is a recommended therapy for VPA toxicity and for VPA-induced delayed cerebral edema because of cytochrome P-450 production of a toxic metabolite of VPA (Stravitz et al., 2013).

Toxicity of VPA could be correlated with the disturbances occurred on the pool of carnitine. But, acylcarnitines are not measured routinely, L-carnitine levels can be used as early indicators of adverse drug reactions (ADRs) and help in prescription of L-carnitine treatment to minimize VPA- induced deficiency of carnitine (McCann et al., 2021).

Aim of the Work

This research aimed to study the effect of VPA on the testes of adult male albino rats, and study the protective effect of both N-acetyl cysteine and L-carnitine on testicular toxicity induced by VPA administration.

Material and Methods

Study design: Experimental study.

Animals:

Sixty (60) adult male albino rats weighing (185 –210 gm) were housed in polypropylene cages under ambient temperature, 21± 3 °C. They were acclimatized to the laboratory condition for one week at the commencement of the treatment protocol. Animals were fed with standard pellet feed and water. The experimental procedure was conducted in accordance with the guide of the care and use of laboratory animals approved by the ethical committee of Sohag University (59/2023-01).

Drugs and its preparation:

1. Sodium valproate 200mg/ml was purchased from SANOFI Company in the form of tablets dissolved in distilled water.
2. Solvent (distilled water) from the SEDICO Company.
3. N-acetyl cysteine from SEDICO Company in the form of pure powder dissolved in distilled water.
4. L-carnitine from MEPACO Company in the form of pure powder dissolved in distilled water.

Time and route of administration: The study was continued for 45 days and the doses taken orally by gavage tube daily.

Animal grouping:

The rats were divided into six groups randomly 10 rats each.

Group I: negative control group which had not received any treatment.

Group II: positive control group which received NAC 150 mg/kg per day (Said and El-Agamy, 2010).

Group III: positive control group had received L-carnitine 500 mg/kg per day (Shaalan et al., 2015).

Group IV: had received VPA 400 mg/kg per day (Shaalan et al., 2015) which equals 40/67 of Ld50 of valproic acid in rats (Budavari, 1989).

Group V: had received VPA 400 mg/kg and NAC 150 mg/kg daily.

Group VI: receive VPA 400 mg/kg and L-carnitine 500 mg/kg daily.

At the end of the experiment, animals of all groups were euthanized; 24 hours after the last dose. The blood samples were collected from jugular vein for chemical analysis of testosterone level. Testes rapidly dissected and excised, rinsed in saline solution, and cut into pieces which were fixed in buffered formaldehyde solution (10%) then embedded in paraffin wax. Sections of 5 microns thickness were mounted on glass slides and stained with hematoxylin and eosin (Hx& E)

Biochemical Tests:

Assessment of hormonal level: By measuring total testosterone level in the serum using Cobase 411 analyzer in the clinical pathology department, faculty of medicine, Sohag University.

Histopathological Examination:

Testes from the experimental rats were fixed in 10% formaldehyde and processed for histopathological examination by light microscopy.

Statistical analysis:

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) using analysis of variance (ANOVA) test and post-hoc test.

Results

This study set out to look into the impact of sodium valproate on the testes of male albino rats, and to compare the possible protective effects of NAC and L-carnitine. Sodium valproate was given in a dose 40/67 of LD50 (400 mg/kg b.wt.).

The present study showed no significant statistical changes in the mean values of rat weights between all studied groups as shown in table (1).

Values of total serum testosterone between the positive control groups and negative control group were investigated to discover if there were possible beneficial or deleterious effects of the commonly used tonics and antioxidants like N-acetyl cysteine, L-carnitine as well as the main study group Na valproate on the testicular function of male albino rats.

Na valproate group had a highly significant decrease in the mean values of total serum testosterone compared to the control one. Comparing the used antioxidants with the control group, there was a significant increase in total serum testosterone level in NAC group and a non-significant increase in L-carnitine group, table 2).

Table (3) showed that there was a highly significant increase in the mean values of total serum testosterone in Na valproate plus NAC and Na valproate plus L-carnitine treated groups in comparison with Na valproate treated group.

The present study also compared both antioxidants with respect to their protective action against the delirious effects of Na valproate on the testes of male albino rats.

Table (4) showed that there was a highly statistically significant increase in the mean of testosterone levels in the Na valproate plus L-carnitine treated group than the Na valproate plus NAC treated group, which points to a higher protective power of L-carnitine than N- acetyl cysteine against the hazardous effect of Na valproate on the testicular function.

Histopathological results:

H & E stained transverse sections of rat testes of the negative control group (group I) revealed sertoli cells together with the normal appearance of the seminiferous tubules lined with several layers of spermatogenic cells. Leydig cells and blood capillaries constitute the interstitial tissue (Figure 1).

Examination of testicular sections of the positive control groups [NAC treated group (group II) (Figure 2) and L-carnitine treated group (group III) (Figure 3)] showed no differences between both groups. Sections revealed normal testicular architecture. The sertoli cells together with the normal appearance of the seminiferous tubules lined with several layers of spermatogenic cells. Leydig cells and blood capillaries constitute the interstitial tissue.

Examination of animal testes treated with valproic acid showed disorganization of the seminiferous tubules. Most of the tubules showed reduced number of spermatogenic cells with

diminished number of layers of spermatogenic cells up to sperms, degenerative changes and hypocellularity of the seminiferous tubules compared to the control and the antioxidant treated groups (II, III) (Figure 4). Also, there is a wide gap between neighboring cells and enlargement of intercellular spaces. Sometimes, interstitial tissue edema and hemorrhage between tubules with decreased number of sperms within the tubular lumen can be seen (Figure 5).

Examination of valproic acid plus NAC treated group (V) showed more organization of all spermatogonic cells with mild edema & congestion as compared to valproic acid treated group with small number of sperms within the lumen of tubules (Figures 6).

Examination of valproic acid plus L- carnitine treated group (group VI) showed preservation of normal structure of seminiferous tubules and nearly normal spermatogenic cord with increasing number of sperms within the lumen of tubules as compared to valproic acid treated group and valproic acid plus NAC group although edema is present (Figures 7).

Table 1: Analysis of Variance (ANOVA) to compare between the studied groups regarding rat weights in studied groups:

Groups	Mean ± SD	P
Negative control (N= 10)	196.3 ± 8.05605	**0.998** ^{NS*}
N-acetyl cysteine (N=10)	196.1 ± 8.2253	
L-carnitine (N=10)	196.3 ± 8.27379	
Na valproate (N =10)	196.3 ± 7.81807	
Na valproate + N-acetyl cysteine (N =10)	196.3 ± 7.63108	
Na valproate + L-carnitine (N =10)	196.3 ± 8.15203	
	196.2667 ± 7.68195	

N: number, SD: Standard deviation, *P-value> 0.05: Non-significant

Table 2: Post-hoc test compare between negative control group and NAC, L- carnitine positive control groups, and Na valproate regarding total serum testosterone.

Groups	Mean ± SD	P
Negative control (N =10)	3.92 ± 0.264869	
N-acetyl cysteine (N =10)	4.204 ± 0.190916	**0.049 S***
L-carnitine (N =10)	4.034 ± 0.22446	**0.422 NS****
Na valproate (N =10)	0.6572 ± 0.368907	**0.001 HS*****

N: number, ** P-value> 0.05: Nonsignificant, *P-value< 0.05 :Significant, *** P-value<0.01: Highly Significant, SD: Standard deviation.

Table 3: Post-hoc test compare Na valproate treated group with both Na valproate plus N-acetyl cysteine, and Na valproate plus L- carnitine treated groups respectively regarding total serum testosterone.

Groups	Mean ± SD	P
Na valproate (N=10)	0.6572 ± 0.368907	
Na valproate + N- acetyl cysteine (N=10)	2.35 ± 0.410041	**0.001 HS*****
Na valproate + L-carnitine (N=10)	3.325 ± 0.364852	**0.001 HS*****

N: number, SD: Standard deviation, *** P-value<0.01: Highly Significant

Table 4: Post-hoc test compare Na valproate + NAC treated group and Na valproate + L-carnitine treated group regarding total serum testosterone.

Groups (N=10)	Mean ± SD	P
Na valproate + N- acetyl cysteine (N=10)	2.35 ± 0.410041	**0.001 HS*****
Na valproate + L-Carnitine (N=10)	3.325 ± 0.364852	

N: number, SD: Standard deviation, *** P-value<0.01: Highly Significant

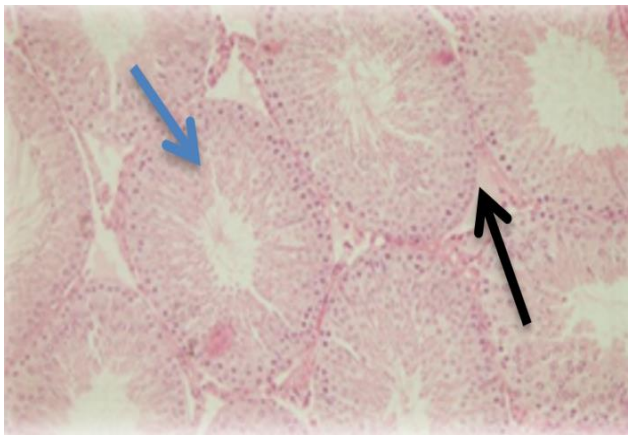

Fig (1): A photomicrograph of transverse section of rat testes showing sertoli cells together with the normal appearance of the seminiferous tubules lined with several layers of spermatogenic cells (blue arrow). Leydig cells and blood capillaries constitute the interstitial tissue (black arrow) (negative control group I) H &E, X200.

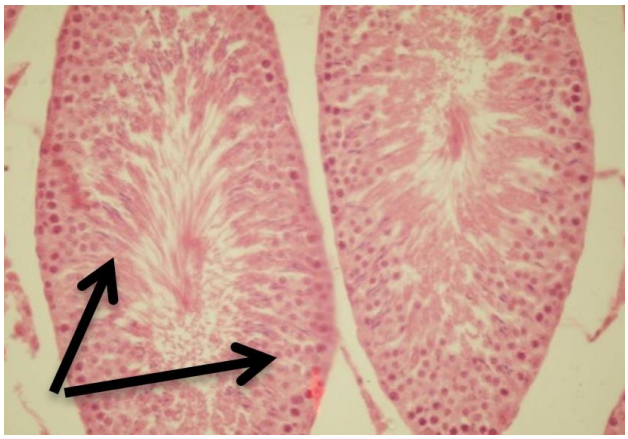

Fig (2): A photomicrograph of transverse section of rat testicular tissue showing sertoli cells together with the normal appearance of the seminiferous tubules lined with several layers of spermatogenic cells (arrows). Leydig cells and blood capillaries constitute the interstitial tissue (positive control group II) H &E, X400.

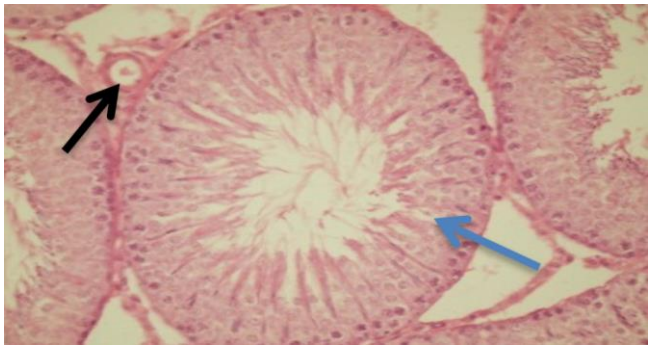

Fig (3): A photomicrograph of transverse section of rat testicular tissue showing sertoli cells together with the normal appearance of the seminiferous tubules lined with several layers of spermatogenic cells (blue arrow). Leydig cells and blood capillaries constitute the interstitial tissue (black arrow) (positive control group III) H&E, X400

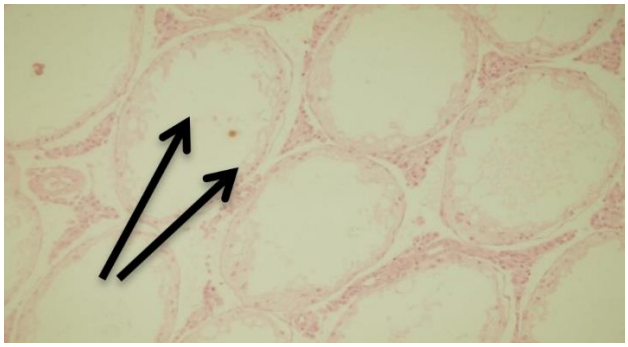

Fig (4): A photomicrograph of transverse section of rat testicular tissue showing reduced number of spermatogenic cells with diminished number of layers of spermatogenic cells up to sperms (arrows) (group IV) H&E, X400.

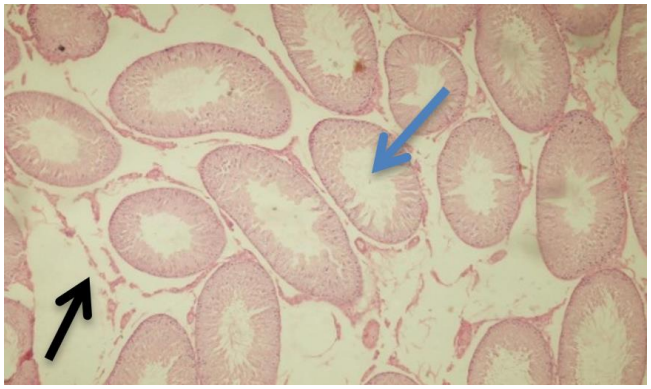

Fig (5): A photomicrograph of rat testicular tissue showing a wide gap between neighboring cells and enlargement of intercellular spaces (black arrow), interstitial tissue edema and hemorrhage between tubules with decreased number of sperms within the tubular lumen (blue arrow) (group IV) H&E, X200.

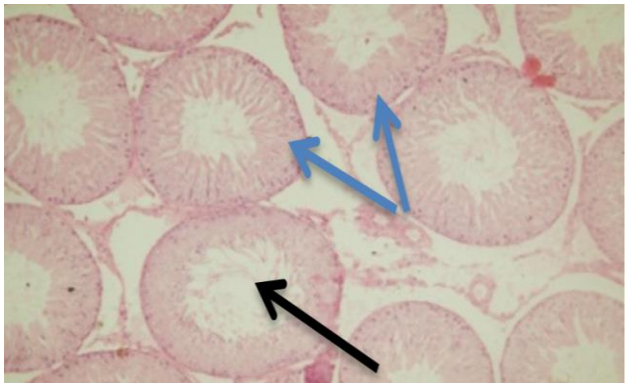

Fig (6): A photomicrograph of rat testicular tissue showing more organization of all spermatogonic cells with mild edema & congestion (blue arrows), with small number of sperms within the lumen of tubules (black arrow) (group V) H&E, X400

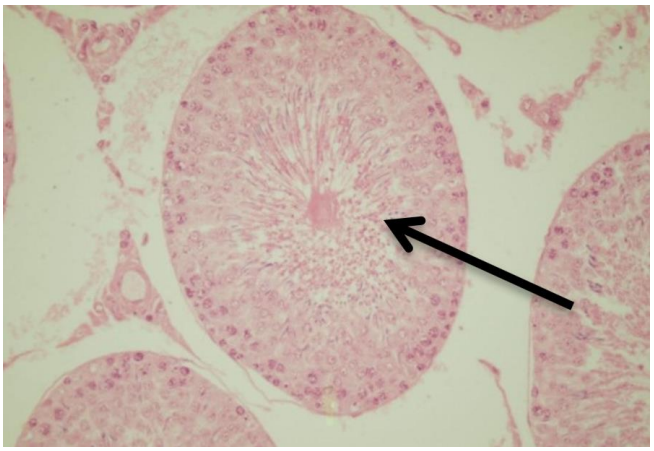

Fig (7): A photomicrograph of rat testicular tissue showing preservation of normal structure of seminiferous tubules and nearly normal spermatogenic cord with increasing number of sperms within the lumen of tubules (arrow) (group VI) H&E, X400

Discussion

Valproic acid (2-propyl-pentanoic acid, VPA) is a broad-spectrum antiepileptic that is used commonly for several neurological and psychiatric problems. It is regarded as an effective antiepileptic medication in a variety of epileptic problems in both children and adults. Although major side effects such hepatotoxicity, hyperammonemic encephalopathy, fatal hemorrhagic pancreatitis, teratogenicity, and bone marrow suppression may happen, it is typically well tolerated. The liver extensively metabolizes VPA to create a variety of metabolites by glucuronic acid conjugation, mitochondrial oxidation, and cytosolic oxidation (Xu et al. 2019).

The aim of this study was to assess the protective effect of N-acetyl cysteine and L-carnitine on testicular toxicity induced by VPA administration.

In the epileptic patients, VPA has been found to interfere with the reproductive endocrine system and lower the quality of semen. They include shrinkage of the prostate, epididymis, and seminal vesicles, as well as decreased or absent spermatogenesis and testicular atrophy (Iamsaard et al., 2017).

Na-valproate is thought to affect the male reproductive system in a dose-dependent manner. Animal studies were employed to detect the toxicity of VPA on reproductive system of adult rats, although VPA is widely used for cases of epilepsy in children as well as adults. Toxicity may be due to oxidative stress and the effect caused by VPA damage to testis which is the principal target organ to oxidative radicals owing to the increased content of polyunsaturated lipid membrane and decreased levels of testosterone due to destruction of germ cells (Manfo et al., 2014). This demonstrates the protective role of the antioxidants NAC and L- carnitine when administered with VPA (Dhouib et al., 2016).

The present study shows a significant statistical decrease in serum testosterone in group IV treated with VPA alone when compared with control group (group I) ($p<0.001$).

The present study confirmed what was previously found by Shelbaya (2016) as a significant decrease ($p<0.05$) in serum testosterone in valproate treated rats after treating with sodium valproate (500mg/kg) for one month.

In harmony with Hamza et al., (2019) the present study showed a significant decrease ($p<0.05$) in serum testosterone in valproate treated rats in a dose of 500 mg/kg orally for one month.

The present study agreed with Vijay et al. (2008) who found that animal groups treated with sodium valproate either 200mg/kg in one group or 400mg/kg in another group for 60 days showed that testosterone level was significantly reduced in both groups ($p<0.001$).

The present study was consistent with Hamza and Amin (2007) who documented that after 7 days of 500mg/kg valproate injection, serum testosterone has significantly declined ($p< 0.001$) compared with the control group along with marked increase in FSH.

On the other side, Røste et al., (2002) found that serum testosterone did not decrease in male wistar rats treated with sodium valproate (200 mg/kg or 400 mg/kg) twice daily each for 90 days. That might be due to different rat species or gradual increase in the dose as their studied animals received half the dose in the first week.

The present study disagreed with Ourique et al. (2016) as they found that valproate administration (400mg/kg) to male wistar rats for one month did not affect serum testosterone level which may be attributed to different duration of the experiment or different species of animal used.

The present study showed a significant statistical increase in serum testosterone in group V compared with group IV ($p<0.001$), which indicated an increase in serum testosterone in animals treated with NAC and valproate in comparison with its level in the group received sodium valproate only.

In contrast, Hamza et al. (2019) showed no increase in serum testosterone in animal group treated with low dose sodium valproate (100 mg/kg plus NAC 100 mg/kg) or in group treated with high dose sodium valproate (500 mg/kg plus NAC 100mg/kg) for one month in comparison with groups treated with valproate alone that may be attributed to different

species of animals used, as they used male wistar rats and different duration of the experiment as the study lasted for one month only.

The present study showed a significant statistical increase in serum testosterone in group VI compared with group IV ($p<0.001$), indicating a higher increase in serum testosterone in animals treated with L- carnitine and valproate than the group received sodium valproate only.

The present study confirmed Shelbaya (2016) previous results as it showed a significant increase ($p<0.05$) in serum testosterone in rats treated with L-carnitine (150 mg/kg) plus sodium valproate (500 mg/kg) for one month in comparison with valproate only treated rats.

Comparing groups V and VI, the present study detected a marked difference of serum testosterone in both groups indicating that serum testosterone was significantly higher ($p<0.001$) in animals treated with valproate plus L-carnitine than in animals treated with valproate plus N-acetyl cysteine.

The present study reveals that animal testes treated with valproic acid showed disorganization of the seminiferous tubules. Most of the tubules showed reduced number of spermatogenic cells with diminished spermatogenic layers to sperms. Degeneration and hypocellularity of the seminiferous tubules comparing it to control or antioxidant treated groups (II, III). Also, there were wide gaps between neighboring cells and enlargement of intercellular spaces. Sometimes, edema of interstitial tissue and hemorrhage between the tubules with decreased number of sperms within the tubular lumen can be found.

Hamza et al., (2019) detected that animal groups treated with low dose sodium valproate (100 mg/kg) showed histopathological changes in testis like degeneration of germ cell, necrosis, edema of tissues, congestion and desquamation with atrophy of the seminiferous tubes. Marked increase in degenerative changes with necrosis was detected in germ cells of rats who administered high dose sodium valproate (500 mg/kg).

Bairy et al., (2010) found that valproate treated animal group (200 mg/kg or 400 mg/kg) showed sloughing of epithelial cells in the lumen of the seminiferous tubules of the testes. In addition to vacuolations seen within the seminiferous tubules in both doses (low and high).

The present study confirmed Girish et al. (2014) findings regarding degeneration and desquamation of epithelium germinal cells in valproate treated rats (400 mg/kg for 7 days).

The present study affirmed Hamza and Amin (2007) study who detected atrophy and degenerations of germ cells in seminiferous tubules. The tubules were shrunken and greatly depleted of germ cells. Between the tubules, leydig cells were depleted and sertoli cells and few germ cells were observed in the lumen of seminiferous tubules. Degenerated leydig cells were also observed between the tubules.

In contrast to the present study Røste et al., (2001) observed that valproate treated wistar rats (200 mg/kg twice daily for 90 days) showed no significant histological difference from control groups. However, the group received high dose valproate (400 mg/kg twice daily for 90 days) showed moderate to severe testicular atrophy. The seminiferous tubules of the animals were mostly atrophic with the most advanced cell type was primary spermatocytes. There was no sign of round spermatids in the tubules. Leydig cells were not affected.

The present study disagreed with Ourique et al. (2016) as their study found that after valproate administration to male Wistar rats (400 mg/kg) for one month, there was no effect on testicular morphology regarding sertoli cells or germ cells. However, the study showed marked deterioration of sperm motility. This difference may be attributed to different duration of the experiment or different animal species brought in the study.

The present study is contradictory to Cansu et al., (2011) whose study; depend on administration of VPA (300 mg/kg) for 90 days to male wistar rats, revealed minimal VPA-associated decrease in cell diameters. In none of the slides analysed there were necrosis, obvious depletion, disorganisation, or exfoliation of germ cells, tubular atrophy, an inflammatory response, or an apparent pathological change in leydig cells. This might be the result of different rat species and drug dosages.

The present study reveals that valproic acid plus NAC treated group (V) showed more organization of all spermatogonic cells with mild tissue edema and congestion as compared to Valproic acid treated group, but there were small number of sperms within the lumen of tubules as compared to valproic acid treated group.

The present study confirmed Hamza et al. (2019) observations regarding an improvement in animals treated with low dose sodium valproate (100 mg/kg) plus NAC (100 mg/kg) in the form of moderate restoration of germ cells. Also seminiferous tubules had multiple spermatogenic cell layers lining them till sperm production; they were bordered with a somewhat swollen stroma. Moreover, those treated with high dose sodium valproate (500 mg/kg) plus NAC (100 mg/kg) showed melioration of germinal cells with decrease of congestion, edema and necrosis.

Turkmen et al. (2019) reported a protective effect of NAC in MK-801in induced testicular toxicity which is an NMDA antagonist. This study found that combined intraperitoneal administration of MK-801 plus NAC for 14 days showed only irregularity at the membrane base of seminiferous tubules in comparison with MK-801 only treated group which showed necrobiotic, degenerative changes in the epithelial cells, vacuole formation within the seminiferous tubules, decreased number of the spermatozoid and disorganization in the basement membrane of the seminiferous tubules of the testes.

Abdelmoaty (2021) found that combined administration of VPA (500mg/kg) and L-cysteine (100 mg/kg) resulted in diminished vacuoles of the inter-

epithelium of seminiferous tubules than that found in VPA only group with normal spermatids and spermatogonia. Compared to group that received VPA treatment, the quantity of spermatozoa in seminiferous tubules increased and the interstitium of testes showed decreased hyalinization with basal layer regulation of seminiferous tubules.

The present study revealed that valproic acid plus L- carnitine treated group (group VI) showed preservation of normal structure of seminiferous tubules and nearly normal spermatogenic cord with increasing number of sperms within the lumen of tubules as compared to valproic acid treated group and valproic acid plus NAC treated group although edema is still present.

The protective role of L-carnitine against testicular damage has been supported by Cabral et al., (2014) study where carnitine had reduced the frequency of apoptotic germ cell and had improved testicular morphology and general function when given to doxorubicin-treated pre-pubertal rats.

To our knowledge, the present study may be the first study to compare protective role of NAC and L-carnitine when administered with VPA. In the present study there was marked improvement upon administration of L-carnitine with VPA in comparison with NAC which improved the results but less than L-carnitine did.

Current study showed also that L-carnitine was more protective than NAC and this could be explained by the fact that VPA administration was associated with deficiency of serum carnitine levels as mentioned by Qiliang et al., (2018). This deficiency concept was proven in the present study by administration of L-carnitine in addition to its antioxidant and enhancing its role on the male reproductive system more than NAC.

This was also supported Okumura et al., (2021) findings who reported that serum free carnitine level in children were normal after supplementation of L-carnitine in comparison with those who did not receive L-carnitine.

Conclusion

Sodium valproate induces testicular toxicity in high doses as 400 mg/kg in adult male albino rats. There is a protective role for both NAC and L-carnitine when either it is administered with VPA. However, L-carnitine has more protective effect than NAC due to its antioxidant effect against free radicals in addition to correction of L-carnitine deficiency that occur with VPA administration due to its effect on carnitine metabolism.

Recommendations

1. Further studies about the protective role of:
   A. L-carnitine against VPA toxicity on other organs like liver, kidney and brain could be done.
   B. L-carnitine, NAC and other antioxidants against VPA induce organ toxicity.
   C. Combined intake of L-carnitine and NAC against VPA induced organ toxicity.
   D. Antioxidants against different doses of VPA.
2. More studies should be conducted on children who are on VPA and study of the long-term protective role of antioxidants.
3. Studies on the effect of antioxidant protective role in cases of acute VPA toxicity should be done

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دراسة التأثير الوقائي لـ ان-اسيتيل سيستايين و ل-كارنيتين علي سمية الخصية المحدثة بإعطاء حمض الفالبرويك في ذكورالفئران البالغة البيضاء

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الملخص العربي

المقدمة: يعد حمض الفالبرويك دواءًا معروفًا مضاد للصرع , وهناك العديد من التأثيرات السامة عن حمض الفالبرويك. **الهدف من الدراسة:** تهدف الدراسة الحالية إلى تسليط الضوء على تأثير حمض الفالبرويك على الخصيتين في ذكور الجرذان البيضاء البالغة ومقارنة التأثير الوقائي لـ ان-اسيتيل سيستايين و ل-كارنيتين على سمية الخصية التي يسببها إعطاء VPA. **الطريقة:** تم إيواء ستين (٦٠) من ذكور الفئران البالغة البيضاء وزنها (١٨٥-٢١٠ جم) وقسمت الفئران إلى ست مجموعات بشكل عشوائي كل مجموعة تحتوي على ١٠ فئران ، المجموعة الأولى (I): مجموعة ضابطة سلبية لم تتلقى أية أدوية. المجموعة الثانية (II): المجموعة الضابطة الإيجابية التي تلقت ١٥٠ مجم /كجم ان-اسيتيل سيستيين يوميًا عن طريق الفم ، المجموعة الثالثة (III): تلقت المجموعة الضابطة الإيجابية ل-كارنيتين ٥٠٠ مجم /كجم يوميًا عن طريق الفم، المجموعة الرابعة (IV): تلقت ٤٠٠ مجم /كجم فالبروات الصوديوم يوميًا عن طريق الفم الذي يساوي ٦٧/٤٠ من Ld50 من حمض الفالبرويك في الفئران، المجموعة الخامسة (V): تلقت ٤٠٠ مجم /كجم فالبروات الصوديوم و ١٥٠ مجم /كجم ان-اسيتيل سيستيين يوميًا عن طريق الفم، المجموعة السادسة (VI): تلقت ٤٠٠ مجم /كجم فالبروات الصوديوم و ل-كارنيتين ٥٠٠ مجم /كجم عن طريق الفم يومياً ولمدة ٤٥ يوم. **النتائج:** أظهرت هذه الدراسة وجود فارق ذو دلالة احصائية بين المجموعة (IV) التي تلقت (VPA) علي شكل انخفاض ملحوظ في هرمون التستوستيرون في الدم مقارنة بمجموعات الضبط (I، II، III)، كذلك مع وجود تغيرات هيستوباثولوجية ملحوظة في المجموعه الرابعة التي تلقت فالبروات الصوديوم مقارنة بالمجموعات الثلاثة الضابطة. وبإضافة مضادات الأكسدة مع فالبروات الصوديوم في نفس الوقت (V، VI)، وجدنا تحسنًا كبيرًا في النتائج المختبرية علي هيئة ارتفاع مستوي هرمون التستوستيرون في الدم مقارنة بمجموعة فالبروات الصوديوم بمفرده (IV)، والتي تتوافق أيضًا مع تحسن النتائج النسيجية الهيستوباثولوجية في

خصي هذه المجموعات. **الخلاصة**: يؤدي فالبروات الصوديوم بجرعات عالية تصل إلى ٤٠٠ مجم / كجم الي تسمم الخصيتين في ذكور الفئران البالغة البيضاء. هناك دور وقائي لكل من ان-اسيتيل سيستيين و ل- كارنيتين عند استخدام كل منهما مع فالبروات الصوديوم وقد بينت نتائج البحث أن الدور الوقائي ل ل- كارنيتين أكبر من ان-اسيتيل سيستايين.

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