Iranian Journal of Toxicology
ARAK UNIVERSITY OF MEDICAL SCIENCES

May 2024, Volume 18, Number 2

Research Paper

Effect of Taurine on Controlling the Side Effects of Valproic Acid in Epileptic Rats

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How to cite this paper:
Hassanein OH, El-Elaimy IA, Bayomy MF, Shehata AM, Ibrahim HM. Effect of Taurine on Controlling the Side Effects of Valproic Acid in Epileptic Rats. Iranian Journal of Toxicology. 2024; 18(2):93-98. **doi:** 10.32592/IJT.18.2.93

doi: 10.32592/IJT.18.2.93

Article info
Received: 04 Jan 2024
Accepted: 19 Apr 2024
Published: 08 May 2024

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ABSTRACT

Background: Valproic acid (VPA) is a well-known antiepileptic drug; however, it has adverse effects on different body organs, particularly as a result of inducing oxidative stress in the liver. Taurine (Tau) is an amino acid prevalent in the brain that possesses anti-tumor, anti-toxic, and antioxidant properties. This study aimed to investigate the potential of the co-treatment of Tau in mitigating the deleterious effects of VPA in pentylenetetrazole (PTZ) epileptic rats.

Methods: A total of 42 rats were divided into six groups of seven as follows: control group, PTZ-treated group (single dose, 60 mg/kg intraperitoneally [IP]), VPA-treated group (500 mg/kg IP for 14 days), Tau-treated group (100 mg/kg orally for 28 days), VPA+PTZ group, and Tau+VPA+PTZ group. The liver function, antioxidant status, and lipid profile markers were evaluated spectrophotometrically.

Results: The IP injection of PTZ and VPA elevated aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma-glutamyltransferase levels. These treatments caused negative alterations in protein concentrations, antioxidant status, and lipid profile markers of the rats' sera. The treatment with Tau+VPA, on the other hand, improved liver function, restored fairly normal total protein and albumin levels, and improved malondialdehyde, glutathione peroxidase, and total antioxidant capacity concentrations. Furthermore, the Tau+VPA treatment significantly controlled total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein levels, compared to the VPA+PTZ treatment.

Conclusion: The treatment with Tau+VPA is highly effective in controlling the unfavorable side effects of VPA in an epileptic rat model.

Keywords: Liver function, Oxidative stress, Pentylenetetrazole, Taurine, Valproic acid

Introduction

Epilepsy occurs as a result of abnormal electrical and synchronous aberrant discharges in the central nervous system (CNS) neurons, manifesting as recurring seizures [1]. Epileptic seizures are associated with changes in the socioeconomic condition, mental health, and behavior of the affected patients [2, 3]. Epilepsy and most antiepileptic drugs may cause oxidative stress due to increases in reactive oxygen species (ROS) in the CNS [4].

Pentylenetetrazole (PTZ) is a common drug for inducing seizures in experimental animals. It is convulsant to the CNS and functions at the picrotoxin sites of the gamma-aminobutyric acid (GABA) receptors, type A. PTZ causes oxidative stress in rats, leading to changes in their antioxidant enzyme status, neuronal damage, and the initiation of epilepsy [5]. Currently available antiepileptic medications are associated with a wide range of side effects, including memory loss, exhaustion, tremors, gastrointestinal issues, osteoporosis, depression, dizziness, and nausea [6]. Antiepileptic drugs, such as valproic acid (VPA) and sodium valproate, raise intracellular ROS levels in tissues such as the liver, brain, and small intestine [7]. The release of intracellular enzymes, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), following VPA treatment is one of the most sensitive and dramatic signs of hepatocyte damage [8]. Based on clinical observations, over 40% of patients taking VPA develop obesity and fatty liver disease [9]. Additionally, VPA treatment results in metabolic and structural changes in the liver [10].

In this study, Tau was used because of its antioxidant and protective effects, which could mitigate the side effects of VPA in PTZ-induced epileptic rats. Tau has many functions in the CNS, ranging from development to cellular protection.

Furthermore, experimental evidence is mounting that the depletion of Tau causes a variety of clinical conditions, including severe cardiomyopathy [11], renal dysfunction [12], and pancreatic malfunction [13]. Besides its neuroprotective qualities, Tau has anti-tumor, anti-toxic, and anti-oxidant properties [14-18]. It also exhibits anti-pyretic and anti-inflammatory effects, benefiting the treatment of hepatic disease [19], diabetes [20], and cardiovascular diseases [21].

Aim of the Study: The current study aims to investigate the potential role of Tau in alleviating the adverse effects of VPA in PTZ-induced epilepsy in an experimental rat model.

Materials and Methods

Experimental Animals: A total of 42 adult male Wistar rats, with an average body weight of 195-200 g, were purchased from a holding company for biological products and vaccines (VACSERA, Cairo, Egypt). All animals were kept in controlled laboratory conditions under 12-hour cycles of dark and light. Standard rodent food and clean water were available to the rats *ad libitum*. For at least nine days prior to the start of the study, the animals were acclimated to the laboratory conditions. Ethical clearance was granted for the study protocol by Menoufia University's Animal Ethics Committee (Approval ID: MUFS/F/PH/1/21). All experimental methods were performed in accordance with relevant and ethical research guidelines.

Chemicals: PTZ, Tau, and VPA were purchased from Sigma Aldrich Chemical Co. (St. Louis, MO, USA). All other chemicals and reagents used in the experiments were of the highest purity.

Experimental Design: To explore the protective effect of Tau against VPA in PTZ-induced rats, the rats were randomly divided into six groups (n=7, each). In the control group, rats were given normal saline (0.9% NaCl) intraperitoneally (IP) for 14 days. In the PTZ-induced group, rats received a single dose of PTZ (60 mg/kg) IP, according to Kapucu *et al.* [22]. In the VPA-treated group, rats were treated with VPA (500 mg/kg) IP for 14 days, according to Tong *et al.* [23]. In the Tau-treated group, rats received a daily oral administration of Tau (100 mg/kg) for 28 days, according to Noor *et al.* [24]. In the VPA+PTZ-treated group, rats were given VPA (500 mg/kg) IP for 14 days and were injected with a single dose of PTZ (60 mg/kg) on the 15th day. In the Tau+VPA+PTZ-treated group, rats received a daily oral dose of Tau (100 mg/kg) for 28 days. They were then treated with VPA (500 mg/kg) IP for 14 days, starting on the 14th day of the study. Finally, they were injected with a single dose of PTZ (60 mg/kg) on the 29th day of the study.

Sample Collection: After sacrificing animals, blood samples were collected and centrifuged at 3000 rpm for 15 min in clean and dry test tubes. The serum samples, as clear supernatants, were aliquoted and stored at -20°C until further analyses.

Estimation of Liver Functions: We performed liver function tests for ALT, AST, alkaline phosphatase (ALP), and gamma glutamyltransferase (GGT) levels using kits from Spectrum Diagnostics (Cairo, Egypt). Total protein and albumin levels of blood samples were determined using colorimetric kits from the same supplier. Globulin levels were also measured by deducting the serum albumin concentrations from the serum total protein [25].

Lipid Profile Estimation: Lipid profile markers, such as total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL), were estimated using Spinreact diagnostic kits (Marid, Spain). The Friedewald equation, which integrates the concentrations of TC, HDL, and TG, was used to determine low-density lipoprotein (LDL) as follows: LDL= TC - (HDL+ VLDL) VLDL= TG/5 [26, 27].

Estimation of Oxidative Stress Parameters: Kits from Bio-diagnostic Co. (Cairo, Egypt) were used to determine the concentration of malondialdehyde (MDA), according to the manufacturer's instructions. The activity of glutathione peroxidase (GPx) and total antioxidant capacity (TAC) were also evaluated by colorimetric assays, according to the manufacturer's protocol (Abcam, Cambridge, UK).

Statistical Analyses: The data were analyzed using SPSS software (version 22) and presented as mean±standard error (SE). A one-way ANOVA was performed to analyze differences among the groups, followed by a post hoc analysis using the least significant difference (LSD) test. Statistical significance was set at $P<0.05$.

Results

Effect of the Combination of Taurine and Valproic Acid on the Liver: Rats treated with PTZ showed significant rises in serum concentrations of AST, ALT, ALP, and GGT, compared to the control group. The injection of VPA also caused significant increases in the concentrations of the four parameters mentioned above. On the other hand, no significant differences were detected after the administration of Tau, compared to the control group. The VPA treatment prior to PTZ significantly increased the concentrations of AST and ALP but caused insignificant rises in the concentrations of ALT and GGT, compared to the PTZ treatment. The oral administration of Tau concurrently with VPA resulted in significant declines in the serum levels of AST, ALT, ALP, and GGT in epileptic rats, compared to the VPA+PTZ treatment (Table 1).

Effect of Taurine and Valproic Acid on Albumin, Globulin, and Total Protein: Table 2 shows the effect of pretreatment with VPA and Taue on total protein, albumin, and globulin levels in PTZ-induced epilepsy rats. The PTZ pretreatment caused significant

reductions in the rats' albumin, globulin, and total protein levels, compared to the control group. Rats treated with VPA alone had significantly lower albumin and total protein levels, without a significant decrease in the globulin level. Rats treated with Tau showed insignificant changes compared to those in the control group. On the other hand, rats pretreated with VPA+PTZ showed a significant decline in total protein and globulin levels, compared to those treated with PTZ alone. The combination of Tau and VPA as a pretreatment improved the total protein and albumin concentrations without a significant difference in the globulin concentration, compared to the VPA+PTZ treatment (Table 2).

Table 1. Effect of the administration of Tau as a co-treatment with VPA on liver function in PTZ-induced epileptic rats

Group	Parameter			
	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)
Control	56.16±1.38	42.83±0.61	42.14±1.32	11.14±0.14
PTZ	129.10±3.86$^{\$}$	127.03±1.49$^{\$}$	168.34±4.41$^{\$}$	15.36±0.39$^{\$}$
VPA	118.26±2.10$^{\$}$	56.71±1.53$^{\$}$	163.66±3.66$^{\$}$	12.10±0.32$^{\$}$
Tau	56.65±2.39	43.48±1.15	41.08±0.91	11.66±0.09
VPA+PTZ	244.32±2.75*	130.88±2.01	230.29±3.74*	15.94±0.24
Tau+VPA+PTZ	149.53±6.07$^{\#}$	60.67±0.64$^{\#}$	110.17±2.82$^{\#}$	11.50±0.31$^{\#}$

Data are represented as mean±SE (n=7). $^{\$}$P<0.05 indicates a significant difference compared to the control group. *P<0.05 indicates a significant difference compared to the PTZ group, and $^{\#}$P<0.05 indicates a significant difference compared to the VPA+PTZ group. (PTZ): pentylenetetrazole, (VPA): valproic acid, (Tau): taurine, (AST): aspartate aminotransferase, (ALT): alanine aminotransferase, (ALP): alkaline phosphatase, (GGT): Gamma-glutamyltransferase (GGT).

Table 2. Effects of the oral administration of Tau as a co-treatment with VPA on albumin, globulin, and total protein concentrations in the sera of PTZ-induced epileptic rats

Group	Parameter		
	Total protein (g/dl)	Albumin (g/dl)	Globulin (g/dl)
Control	7.02±0.23	3.81±0.06	3.21±0.24
PTZ	5.43±0.15$^{\$}$	2.76±0.13$^{\$}$	2.66±0.25$^{\$}$
VPA	6.05±0.05$^{\$}$	3.04±0.15$^{\$}$	3.01±0.16
Tau	7.29±0.09	3.67±0.08	3.62±0.08
VPA+PTZ	4.06±0.05*	2.73±0.11	1.33±0.13*
Tau+VPA+PTZ	4.88±0.12$^{\#}$	3.36±0.02$^{\#}$	1.53±0.13

Data are represented as mean±SE (n=7). $^{\$}$P<0.05 indicates a significant difference compared to the control group. *P<0.05 indicates a significant difference compared to the PTZ group, and $^{\#}$P<0.05 indicates a significant difference compared to the VPA+PTZ group. (PTZ): Pentylenetetrazole, (VPA): Valproic acid, (Tau): Taurine.

Effects on Lipid Peroxidation and Total Antioxidant Capacity: The data presented in Table 3 reflect the effect of treatment with Tau+VPA on lipid peroxidation, GPx, and TAC in the sera of PTZ-kindled rats. Animals injected with either PTZ or VPA showed significant increases in their MDA levels, accompanied by significant decreases in GPx and TAC, compared to the control group. On the other hand, no significant differences were found following the administration of Tau, compared to the control group. Data from the rats in the VPA+PTZ group showed significant increases in MDA levels without notable changes in the TAC and/or GPx levels, compared to the rats treated with PTZ alone. The treatment with Tau+VPA resulted in a significant decline in MDA levels and significant rises in TAC and GPx levels, compared to the VPA+PTZ treatment (Table 3).

Effect of Taurine Combined with Valproic Acid on Lipid Profile Parameters: Table 4 presents the effect of Tau+VPA on the lipid profile of PTZ-treated rats. Animals treated with PTZ or VPA showed significant increases in TC, TG, and LDL and a significant decline in their HDL, compared to the control group. The administration of Tau caused insignificant changes, compared to those found in the control group. The combination of VPA and PTZ showed significant increases in TC, TG, and LDL levels and a significant decrease in the HDL level, compared to those treated with PTZ alone. The treatment of rats with Tau+VPA significantly improved TG and HDL serum levels and almost restored TC and LDL concentrations, compared to the treatment with VPA alone (Table 4).

Table 3. Effects of the administration of Tau as a co-treatment with VPA on MDA, GPx, and TAC levels in the sera of PTZ-induced epileptic rats

Group	Parameter		
	MDA (nmol/ml)	GPx (nmol/ml)	TAC (nmol/ml)
Control	2.60±0.12	30.96±0.80	6.78±0.26
PTZ	4.18±0.11$^{\$}$	19.03±0.30$^{\$}$	2.94±0.08$^{\$}$
VPA	3.78±0.07$^{\$}$	19.95±0.41$^{\$}$	3.20±0.11$^{\$}$
Tau	2.57±0.13	32.05±0.73	7.20±0.25
VPA+PTZ	4.74±0.10*	18.91±0.29	2.84±0.07
Tau+VPA+PTZ	2.64±0.15$^{\#}$	22.27±0.67$^{\#}$	4.37±0.16$^{\#}$

Data are represented as mean±SE (n=7). $^{\$}$P<0.05 indicates a significant difference compared to the control group. *P<0.05 indicates a significant difference compared to the PTZ group, and $^{\#}$P<0.05 indicates a significant difference compared to the VPA+PTZ group. (PTZ): pentylenetetrazole, (VPA): valproic acid, (Tau): taurine, (MDA): malondialdehyde, (GPx): glutathione peroxidase, (TAC): total antioxidant capacity.

Table 4. Effects of the administration of Tau as a co-treatment with VPA on lipid profile in PTZ-induced epileptic rats

Group	Parameter			
	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
Control	61.50±1.53	42.54±0.45	21.90±0.54	30.99±0.82
PTZ	100.16±2.08$^{\$}$	85.10±0.83$^{\$}$	17.09±0.38$^{\$}$	66.27±1.62$^{\$}$
VPA	83.02±1.78$^{\$}$	100.30±2.57$^{\$}$	17.34±1.02$^{\$}$	46.05±2.28$^{\$}$
Tau	61.20±1.30	45.08±0.53	20.78±0.59	35.23±1.30
VPA+PTZ	126.08±1.73*	154.80±8.36*	12.72±1.02*	87.72±3.57*
Tau+VPA+PTZ	65.49±1.77$^{\#}$	55.49±0.58$^{\#}$	19.86±0.39$^{\#}$	34.79±1.15$^{\#}$

Data are represented as mean±SE (n=7). $^{\$}$P<0.05 indicates a significant difference compared to the control group. *$P<0.05$ indicates a significant difference compared to the PTZ group, and $^{\#}$P<0.05 indicates a significant difference compared to the VPA+PTZ group. (PTZ): Pentylenetetrazole, (VPA): Valproic acid, (Tau): Taurine, (TC): Total cholesterol, (TG): Triglycerides, (HDL): High-density lipoprotein, (LDL): Low-density lipoprotein.

Discussion

In the present study, treatment with PTZ resulted in deleterious changes in the rats' liver function, lipid profile, peroxidation, and antioxidant levels. These results are consistent with the findings reported by previous studies [28-30]. VPA, or its sodium salt (Na^+ Valproate), has a number of side effects on several human organs, including the liver. In this study, VPA-treated rats had significantly higher AST, ALT, ALP, and GGT levels than the controls. Specifically, the VAP+PTZ treatment had a damaging effect on the rats' liver function. In this context, VPA treatment increased the liver enzymes in the sera, which is attributable to damaged hepatocytes and/or apoptosis due to oxidative stress [31, 32]. Furthermore, studies have proposed that the metabolism of VPA accumulates hazardous metabolites and lipid peroxidation, thereby preparing the ground for abnormal liver responses [33, 34].

In the current study, Tau was administered together with VPA, which might have led to elevated levels of AST, ALT, ALP, and GGT in PTZ-treated rats. In a previous study on rats treated with ethanol and/or carbon tetrachloride, Tau reduced liver damage by lowering ALT and AST levels [35]. A previous study by Hagar (2004) demonstrated the protective effects of Tau against cyclosporine-A in rats based on improvements in AST, ALT, and GGT levels [36]. Possibly, the hepatoprotective effects of Tau are partly due to its antioxidant properties [37].

In 2015, Shaalan *et al*. reported that VPA treatment resulted in a significant drop in serum albumin, globulin, and total protein levels [38]. These findings are partially consistent with our results, which show that VPA treatment alone in rats has resulted in considerable declines in serum albumin and total protein levels [39, 40]. The dramatic effects of VPA may be due to its induction of oxidative stress, which is believed to be a contributing factor to the etiology of some liver disorders [41]. In 2019, Shen *et al*. proposed metabolic pathways that differentiated the Tau-supplemented groups from the control group in fish. These pathways included the tricarboxylic acid cycle, urea cycle, choline, and purine metabolism. Additional pathways included amino acid metabolism, protein digestion and absorption, glycerophospholipid metabolism, and ATP-binding transporters [42]. These findings underscore the role of Tau in the maintenance and enhancement of critical biochemical pathways. Compared to the VPA+PTZ group, the co-treatment with Tau improved albumin and total protein levels, while its effects on globulin levels were insignificant. In cyclosporine-treated rats, the Tau treatment improved the total protein levels [36].

In the current study, the administration of VPA resulted in significant declines in GPx and TAC levels and a significant rise in MDA levels. Rats treated with VPA+PTZ showed a significant rise in their MDA levels without notable changes in GPx or TAC, compared to those treated with PTZ alone. Our results also align with those of Shaalan et al. (2015) and Chaudhary and Parvez (2012), revealing that treatment with VPA resulted in significant decreases in catalase, superoxide dismutase, and GPx and a significant increase in MDA levels in rats treated with VPA [38, 43]. Previous studies have indicated that treatment with VPA stimulated the generation of ROS [23,33], which might be a determinative factor in the depletion of antioxidants while simultaneously raising lipid peroxidation. The VPA treatment was also found to reduce erythrocyte GPx, catalase, glutathione reductase, and glutathione S transeferase in children and adult patients [44].

In this study, pretreatment with Tau+VPA resulted in a significant decline in MDA levels while causing significant rises in TAC and GPx levels, compared to the treatment with VPA+PTZ. Previous studies have also shown similar results to those of the current study following the Tau treatment. Another study has reported that treatment with Tau in carbon tetrachloride-exposed rats reduced MDA levels but increased SOD and GPx levels in their tissues and erythrocytes [45]. Gürer et al. (2001) demonstrated the antioxidant effect of Tau in rats treated with lead acetate, leading to a decrease in MDA while increasing glutathione levels [46]. Tau has been shown to act as a direct antioxidant in tissues such as the liver, scavenging oxygen-free radicals and thereby preventing lipid peroxidation. It also serves as an indirect antioxidant by lowering the cell membrane permeability via oxidative damage [47].

In this study, treating rats with VPA significantly increased the level of lipid profile parameters, such as TC, TG, and LDL, while significantly decreasing the level of HDL. In this context, Lahneche et al. (2017) reported that VPA-treated rats exhibited significantly higher TC and TG levels than the control animals [8].

Previous to that study, Hamza et al. (2015) reported that rats receiving varying doses of sodium valproate showed a marked increase in their lipid profile markers, such as TC, TG, and LDL, together with a significant decline in the serum HDL level [32].

The metabolism, synthesis, and transportation of lipids are critical functions of the liver. As a result, people with significant liver disorders usually manifest an abnormal lipid profile [48]. It has been reported that sodium valproate depletes the level of α-ketoglutarate [49,50], leading to elevated serum acetyl CoA levels, which are involved in the synthesis of fatty acids and TC [32]. PTZ-treated rats that received the Tau+VPA treatment showed improvements in their lipid profile parameters. Balkan et al. (2002) demonstrated the effect of Tau on lipids in rats pretreated with ethanol. These authors reported that the Tau treatment decreased the rats' total lipid and TG levels [51].

Furthermore, in women with type 2 diabetes, total-body resistance exercise training combined with Tau supplementation was found to reduce TG and TC while increasing the HDL level more than those in other groups [52]. There have been proposed pathways involved in Tau's hypolipidemic effects via the enhancement of cholesterol catabolism into bile acids that can promote LDL depletion in the liver [53]. These events are likely to reduce the hepatic cholesterol ester pool and enhance LDL receptor upregulation and apolipoprotein B secretion while suppressing LDL and very-low-density lipoprotein synthesis and release [54].

Conclusions

The current study revealed that pretreatment with Tau+VPA prior to the injection of PTZ is promising, potentially mitigating various negative biochemical impacts of VPA in PTZ-treated rats. This improvement is possibly due to Tau's role in controlling liver function, antioxidant status, and lipid profile parameters.

Name of the institution where the study was conducted: Zoology Department, Faculty of Science, Menoufia University, Shebin El-Kom, Meoufia, Egypt.

Conflict of Interests

The authors declare that they have no conflict of interest with any internal or external entities.

Funding

This study was solely funded by the authors.

Acknowledgement

We would like to thank Dr. Ahmed M. Ashour, Central Lab, Faculty of Science, Menoufia University, for his valuable contributions to conducting laboratory experiments.

Compliance with Ethical Guidelines

Ethical clearance was granted for the current study by Menoufia University's Institutional Animal Research Ethics Committee (Approval ID: MUFS/F/PH/1/21). All methods were performed in accordance with relevant guidelines and regulations.

Authors' Contributions

Conceptualization: O.H.H., I.A.E, M.F.F.B, A.M.S.; Methodology: O.H.H.; First draft: O.H.H., H.M.I; Final draft, review, and supervision: O.H.H., H.M.I. All authors reviewed and approved the final version of the manuscript.

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