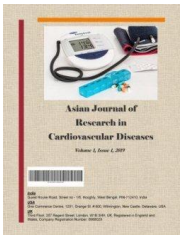

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Effects of Valproic Acid Administration on Cardiovascular Risk Factors in Male Albino Rats

Abiodun Olusoji Owoade [a*], Adewale Adetutu [a], Temitope Deborah Olaniyi [a] and Akinade William Owoade [b]

[a] Department of Biochemistry, Ladoke Akintola University of Technology, Ogbomosho, Nigeria.
[b] Department of Biochemistry, College of Medicine, University of Ibadan, Ibadan, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Valproic acid (VPA) is an antiepileptic drug with a well-documented hepatotoxic effect among other several side effects. However, the effect of valproic acid administration on lipid profile and cardiovascular risk factors remains inconclusive and highly controversial.
Method: In order to investigate the effects of valproic acid on lipid profile, male albino rats were treated with valproic acid at a dose of 7.14 mg/kg body weight intraperitoneally for two and four weeks while a group was allowed to recover for seven days after four weeks of valproic acid administration.
Results: Administration of valproic acid induced dyslipidemia in different compartments of the animals under investigation. Hypocholesterolemia characterized the effect of valproic acid administration in the LDL+VLDL while hypertriglyceridemia was the hallmark of its effect in all blood compartments although hypertriglyceridemia effect drops significantly when rats were allowed to recover for 7 days. In the tissues, valproic acid administration did not significantly affect cholesterol and triglyceride levels but phospholipid levels in the heart and kidney were significantly decreased by 46.03% and 38.57% after 2 weeks of administration while phospholipid levels in other tissues compartment were not affected.
Conclusion: The results presented in this study are in support of the argument that valproic acid administration does not significantly affect lipid profile because the perturbations of lipid content observed are non-lipotoxic and may not pose a cardiovascular disease risk.

**Corresponding author: E-mail: aoowoade@lautech.edu.ng;*

Keywords: Valproic acid; hepatotoxic; hypocholesterolemia; hypertriglyceridemia.

1. INTRODUCTION

"Valproic acid (VPA) is an antiepileptic drug that is widely used in the treatment of epileptic children and is effective against many types of seizure disorders either alone or as a component of a multidrug regimen" [1]. "Valproic acid (2-propylpentanoic acid) is a branched short-chain fatty acid derived from valeric acid which is extracted from Valeriana officinalis" [2,3]. Valproic acid is well absorbed with plasma therapeutic levels of approximately 40–100 µg/ml or 280–700 µmol /L after long-term use [4]. "In epilepsy control, it has been suggested that VPA acts via many mechanisms, the most predominant being the enhancement of the inhibitory GABAergic activity and the inhibition of glutamatergic transmission modulating sodium and potassium channels" [5,6].

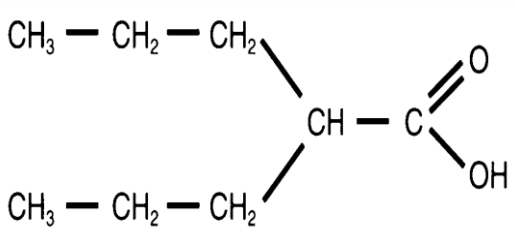

Fig. 1. Structure of valproic acid

"Valproic acid has several side effects, such as weight gain, blood dyscrasias, and liver injury" [7]. "Its long-term use is associated with metabolic disorders such as hyperinsulinemia, insulin resistance, hyperleptinemia and leptin resistance resulting in weight gain, dyslipidemia, menstrual irregularities, hyperandrogenism and polycystic ovarian syndrome" [8]. Although the hepatotoxic effects of valproic acid are well documented, the little information available on the effects of valproic acid on lipid metabolism are inconclusive and highly controversial [8]. "Several studies have found that valproic acid does not affect total cholesterol levels, as well as other lipid profiles" [8-10], "while other studies have shown significant changes in lipid, lipoprotein and apolipoprotein profiles" [9-11].

It is however important to have a clear view of the effect of valproic acid on lipid metabolism because lipids play a major role in the pathogenesis and progression of many disease conditions [12]. "Dyslipidemia is known to be an important risk factor for atherosclerosis. Cholesterol has an important role in the process of atherosclerosis by increasing endothelial permeability, lipoprotein retention in blood vessels, recruitment of inflammatory cells and the formation of foam cells" [8,13]. "In addition, dyslipidemia is presently a major factor to be considered in assessing the safety of new drugs and earlier approved drugs" [14]. Therefore, the present study was an attempt to investigate the effects of administration of therapeutic doses of valproic acid on lipid metabolism.

2. MATERIALS AND METHODS

2.1 Chemicals

Valproic acid was a product of Sigma-Aldrich, Missouri, USA. All other chemicals used in this study were of the purest grade available and were obtained from British Drug House (BDH) Chemicals Limited, Poole, England and Sigma-Aldrich, Missouri, U. S. A.

2.2 Animals and Treatment

Twenty–four (24) male Wistar strain albino rats with body weights between 180 and 200 g were obtained from the Experimental Animal Unit of the Faculty of Agriculture, Ladoke Akintola University of Technology, Ogbomoso, Nigeria. All rats were kept in cages in a room maintained at 26–29 °C with a 12-hour light-dark cycle for 3-weeks to acclimatize and were allowed free access to food and water *ad libitum*. The faculty of basic medical science, Ladoke Akintola University of Technology, Ogbomoso, research ethics committee gave ethical approval for the study (FBMS2020/005). The animals were divided into four groups of six animals per group. Three groups were treated with valproic acid at 7.14 mg/kg body weight, 24 hourly for 14 and 28 days respectively. Valproic acid was constituted in saline solution, prepared fresh and administered in a total volume of 0.1 mL through the intraperitoneal route. Control animals received an equivalent volume of saline solution 24 hourly. The animals were given free access to food and distilled water during the experiment. At the end of the valproic acid treatment and 7 days after the discontinuation of the valproic

acid, blood was collected from the animals into heparinised tubes by cardiac puncture under light ether anaesthesia after an overnight fast. The animals' livers, kidneys, brains, hearts, lungs, and spleens were removed for biochemical analysis. Plasma and red blood cells were separated from blood samples by centrifugation. All samples were kept at -20°C until they were analyzed.

2.3 Biochemical Analyses

2.3.1 Plasma lipid profile

"Plasma concentrations of total cholesterol and triglycerides were determined with commercial kits (CYPRESS® Diagnostics, Langdorp, Belgium.). HDL cholesterol and triglycerides were determined in plasma with the same commercial kits for total cholesterol and triglycerides after very-low-density lipoproteins (VLDL) and LDL were precipitated with heparin-$MnCl_2$ solution" [15]. "Total phospholipids in plasma were extracted with the chloroform-methanol mixture (2:1, v/v)" as described by Folch et al. [16]. "Phospholipid content was then determined" as described by Stewart [17]. Briefly, an aliquot of the phospholipid extract was evaporated to dryness at 60°C. 2 ml chloroform was added to the dried lipid extract after cooling and vortexed. The liquid was then vortexed for 1 minute after adding 2 mL of ammonium ferrothiocyanate. The phases were allowed to split for 10 minutes. The absorbance of the chloroform layer was measured at 488 nm. The concentrations of phospholipids were then calculated using a phospholipid standard as a reference.

2.3.2 Erythrocyte lipid profile

"Because the Folch extraction [16] produced lipid extracts that were highly pigmented", "an improved procedure for the extraction of lipids from erythrocytes using chloroform isopropanol (7:11, v/v) described by Rose and Oklander [18] was employed". "For the determination of cholesterol, an aliquot of the chloroform-isopropanol extract was evaporated to dryness at 60°C. Triton X-100/ chloroform mixture (1:1, v/v, 20 µl) was added to resolve the lipids and again the solvent was evaporated"[18]. "Then 1 ml of commercially available cholesterol kit reagent (CYPRESS® Diagnostics, Langdorp, Belgium.) was added and vortexed. After incubation in the dark at room temperature for 30 min, cholesterol content was determined by colourimetry" [19]. "Determination of total phospholipids and free fatty acids in the chloroform-isopropanol extract of the erythrocyte followed the same procedure as described for plasma" [17].

2.3.3 Organ lipid profile

"Lipids were extracted from the organs (liver, kidney, brain, heart, lung and spleen)" as described by Folch et al. [16]. "After washing with 0.05M KCl solution, aliquots of the chloroform-methanol extract were then used for the determination of cholesterol, triglycerides and phospholipids concentrations. Cholesterol was determined in an aliquot of the chloroform-methanol extract of each organ as described for erythrocytes while the determination of phospholipids followed the same procedure as described for plasma. Triglyceride concentrations in aliquots of the chloroform-methanol extracts of each organ were determined following the procedure" described by Kriketos et al. [20]. "Briefly, an aliquot of the chloroform-methanol extract in Eppendorf tubes was evaporated to dryness at 60°C. After cooling, 200 µl of ethanol (97%) was added to the tube to re-suspend the triglyceride. Then 1 ml of commercially available triglyceride kit (CYPRESS® Diagnostics, Langdorp, Belgium) was added and vortexed. After incubating in the dark at room temperature for 20 min, triglyceride content was determined spectrophotometrically" [20].

2.4 Statistical Analysis

Results are expressed as mean S.E.M. The levels of homogeneity among the groups were assessed using One-Way Analysis of Variance (ANOVA) followed by Tukey's test. All analyses were done using Graph Pad Prism software Version 5.00 and p values < 0.05 were considered statistically significant.

3. RESULTS

3.1 Effect of Valproic Acid on Plasma Lipid Profile of the Animals

The results of the study presented in Fig. 2 depict the effects of valproic acid on the plasma lipid profile of the animals. Administration of valproic acid did not significantly affect the cholesterol concentration. However, triglyceride and phospholipid concentrations of all the animals were significantly ($p < 0.05$) increased

by valproic acid administration with plasma triglyceride concentration increased by 80.52% and 120.24% respectively and plasma phospholipid concentration increased by 48.43% and 50.33% respectively after 2 and 4 weeks of valproic acid administration when compared with control rats. Plasma triglyceride concentration returned to normal after valproic acid administration was discontinued for 7 days while plasma phospholipid sustained the increase.

3.2 Effect of Valproic Acid on HDL Lipid Profile of the Animals

Administration of valproic acid had no significant effect on HDL cholesterol concentrations. However, valproic acid administration significantly increased HDL triglyceride and phospholipid concentrations with HDL triglyceride concentration increased by 2.5 fold and 5.1 fold respectively and HDL phospholipid concentration increased by 2.1 fold and 2.4 fold after 2 and 4 weeks of valproic acid administration when compared with control rats. The lipids concentration was sustained after discontinuation of Valproic acid treatment.

3.3 Effect of Valproic Acid on LDL+VLDL Lipid Profile of the Animals

The results of the LDL+VLDL fraction is presented in Fig. 4. Administration of valproic acid resulted in a significant decrease ($p < 0.05$) in LDL+VLDL cholesterol, triglyceride and phospholipid concentrations except for LDL+VLDL triglyceride concentration which was increased significantly after 2 weeks of valproic acid administration when compared with control rats. The decrease in LDL+VLDL cholesterol, triglyceride and phospholipid concentrations obtained after 4 weeks of treatment was sustained 7 days after discontinuation of the drug.

3.4 Effect of Valproic Acid on Erythrocyte Lipid Profile of the Animals

The effects of valproic acid on the lipid profile of the erythrocyte is depicted in Fig. 5. Valproic acid treatment for 2 and 4weeks significantly increased triglyceride concentration by 61.58% and 87.11% respectively while

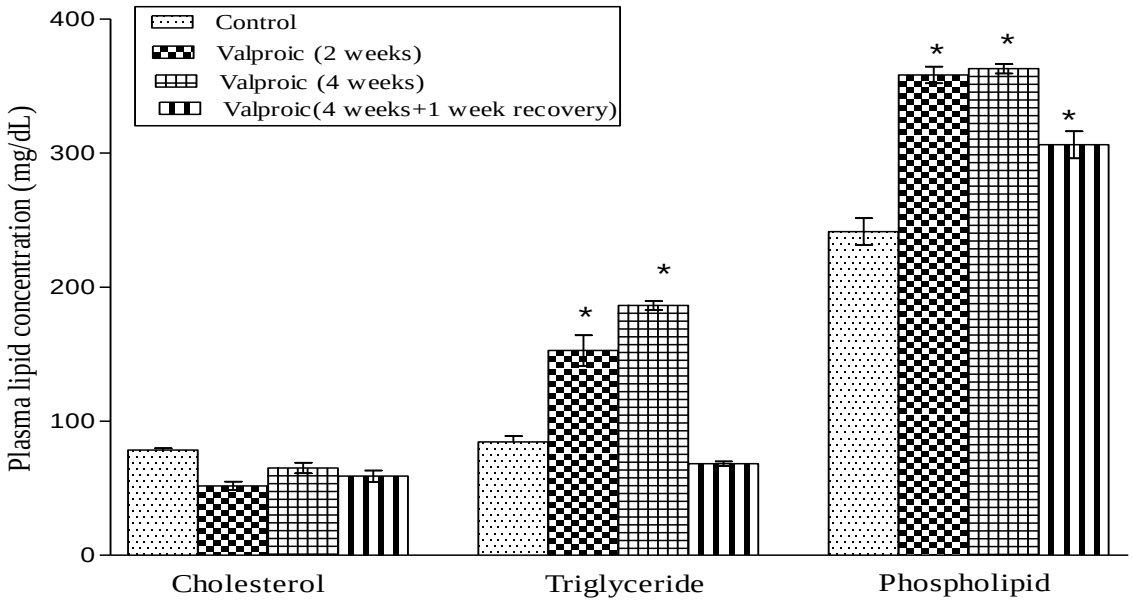

Fig. 2. Effect of valproic acid on plasma lipid profile of the animals

*Each point represents mean ± SEM of 6 animals. The significant difference ($p < 0.05$) between the control group and valproic acid administered groups are represented by **

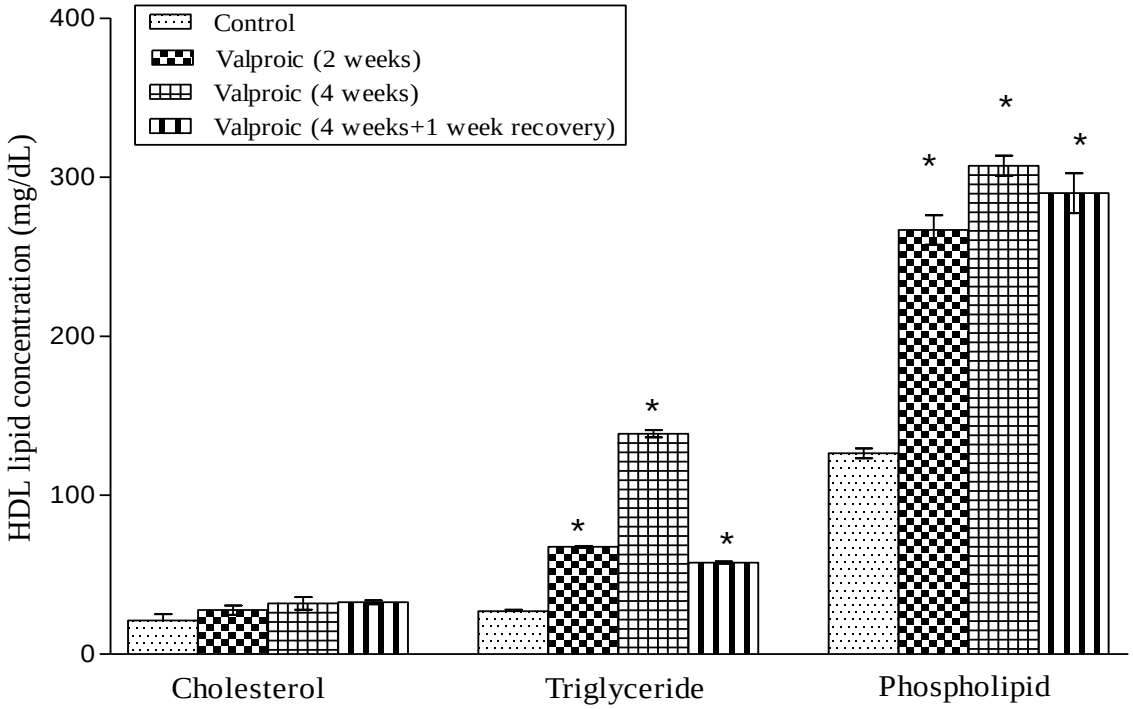

Fig. 3. Effect of valproic acid on HDL lipid profile of the animals

*Each point represents mean ± SEM of 6 animals. The significant difference (p < 0.05) between the control group and valproic acid administered groups are represented by **

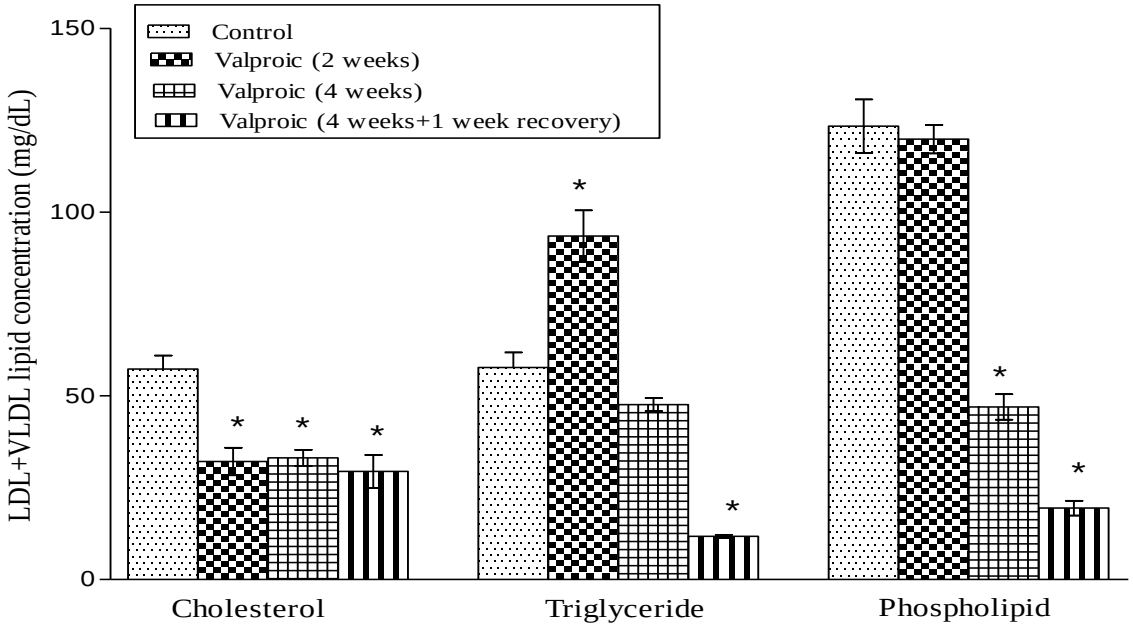

Fig. 4. Effect of valproic acid on LDL+VLDL lipid profile of the animals

*Each point represents mean ± SEM of 6 animals. The significant difference (p < 0.05) between the control group and Valproic acid administered groups are represented by **

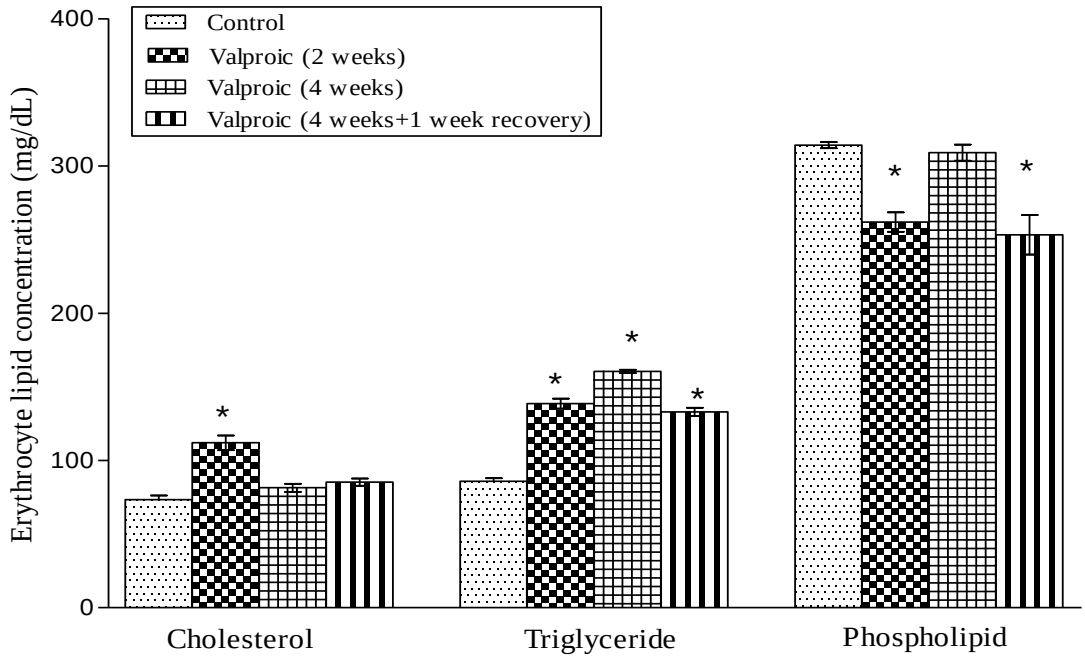

Fig. 5. Effect of Valproic acid on erythrocyte lipid profile of the animals

*Each point represents mean ± SEM of 6 animals. The significant difference (p < 0.05) between the control group and valproic acid administered groups are represented by **

cholesterol concentration was significantly increased by 52.49% after 2 weeks only and its value returned to normal in the subsequent weeks when compared with control rats. Administration of Valproic acid significantly (P < 0.05) decreased erythrocyte phospholipid after 2 weeks of administration and the decrease was sustained after 7 days of recovery when compared with control rats.

3.5 Effect of Valproic Acid on Liver, Kidney and Heart Lipid Profiles of the Animals

The mean values of the liver, kidney and heart lipid profiles are shown in Table 1. Administration of valproic acid resulted in a significant ($p < 0.05$) decreased in phospholipid concentration with heart phospholipid concentration decreased by 30.02% and 46.03% respectively after 2 and 4 weeks when compared with control rats. Valproic acid treatment for 2 and 4 weeks did not significantly affect cholesterol and triglyceride concentrations although heart cholesterol was increased by 7.55% and 28.77% respectively and liver triglyceride was decreased by 25.57% and 32.15% respectively when compared with control rats.

3.6 Effect of Valproic Acid on Brain, Lung and Spleen Lipid Profiles of the Animals

The mean values of the brain, lung and spleen lipid profiles are shown in Table 2. Administration of valproic acid resulted in a significant ($p < 0.05$) decreased in brain cholesterol concentration by 37.01% after 2 weeks and a decrease in brain triglyceride concentration by 24.57% after 4 weeks, while lung and spleen cholesterol and triglyceride concentrations were not affected by valproic acid treatment. Administration of valproic acid significantly affected phospholipid concentration after 2 weeks, with brain phospholipid concentration decreased by 25.31%, lung phospholipid concentration decreased by 18.97% and spleen phospholipid concentration increased by 18.25% when compared with control rats.

4. DISCUSSION

"A vast amount of evidence has confirmed that lipid and lipoprotein abnormalities play a major role in the pathogenesis and progression of atherosclerosis and cardiovascular diseases" [21-23]. "These chronic degenerative disorders

have become a growing health problem worldwide. Dyslipidemia is known to be an important risk factor for cardiovascular disease and increasing incidents of sudden death due to cardiovascular disease among the African population in both urbanized and underdeveloped rural community is of great concern" [24]. Therefore, this present study evaluated the distribution of some blood lipids in a population of rats that are treated with valproic acid, an anticonvulsive drug. A major finding of this study was that valproic acid administration perturbs the metabolism of lipids in different compartments of the organism. These perturbations were reflected as up/down regulation of the concentrations of the major lipids (cholesterol, triglycerides, and phospholipids).

"Cholesterol is a modified steroid, a fat-like substance that occurs naturally in all parts of the body. It is also an essential structural component of the animal cell that is required to establish proper membrane fluidity and permeability" [25]. "Cholesterol is known to play an important role in the process of

Table 1. Effect of Valproic acid on liver, kidney and heart lipid profile of the animals

Treatment	Liver	Kidney	Heart
Cholesterol			
Control	3.70 ± 0.08	3.64 ± 0.09	1.99 ± 0.17
Valproic (2 weeks)	3.38 ± 0.08	2.77 ± 0.19	2.14 ± 0.24
Valproic (4 weeks)	3.51 ± 0.07	2.96 ± 0.16	2.56 ± 0.24
Valproic (4 weeks + 1 week recovery)	3.23 ± 0.06	3.07 ± 0.14	3.09 ± 0.27
Triglyceride			
Control	3.89 ± 0.61	3.11 ± 0.11	8.23 ± 0.62
Valproic (2 weeks)	2.89 ± 0.09	3.52 ± 0.24	7.92 ± 0.54
Valproic (4 weeks)	2.64 ± 0.23	3.85 ± 0.20	8.27 ± 0.36
Valproic (4 weeks + 1 week recovery)	1.66 ± 0.02	3.66 ± 0.09	7.38 ± 0.28
Phospholipid			
Control	49.47 ± 2.44	44.93 ± 0.68	41.60 ± 1.87
Valproic (2 weeks)	48.84 ± 1.29	32.52 ± 1.19*	29.11 ± 0.31*
Valproic (4 weeks)	37.70 ± 2.98*	27.60 ± 1.02*	22.45 ± 0.41*
Valproic (4 weeks + 1 week recovery)	42.75 ± 2.89	32.64 ± 0.26*	15.75 ± 0.42*

*Each point represents mean ± SEM of 6 animals. The significant difference ($p < 0.05$) between the control group and valproic acid administered groups are represented by **

Table 2. Effect of valproic acid on brain, lung and spleen lipid profile of the animals

Treatment	Brain	Lung	Spleen
Cholesterol			
Control	19.75 ± 0.78	6.16 ± 0.59	1.901 ± 0.01
Valproic (2 weeks)	12.44 ± 0.32*	8.65 ± 0.59	1.43 ± 0.07
Valproic (4 weeks)	17.27 ± 0.52	7.64 ± 0.66	1.57 ± 0.09
Valproic (4 weeks + 1 week recovery)	18.24 ± 0.74	8.99 ± 0.72	1.95 ± 0.03
Triglyceride			
Control	3.46 ± 0.75	7.10 ± 0.42	7.57 ± 0.17
Valproic (2 weeks)	3.79 ± 0.14	5.44 ± 0.31	8.22 ± 0.06
Valproic (4 weeks)	2.61 ± 0.16	6.24 ± 0.48	9.06 ± 0.30
Valproic (4 weeks + 1 week recovery)	1.22 ± 0.03	7.69 ± 0.57	9.46 ± 0.09
Phospholipid			
Control	49.19 ± 2.75	49.75 ± 2.40	26.57 ± 0.42
Valproic (2 weeks)	36.74 ± 1.69*	40.31 ± 3.85*	31.42 ± 0.84*
Valproic (4 weeks)	38.66 ± 3.23*	57.06 ± 0.72	25.33 ± 2.09
Valproic (4 weeks + 1 week recovery)	45.14 ± 1.26	52.60 ± 3.35	31.06 ± 2.06

*Each point represents mean ± SEM of 6 animals. The significant difference ($p < 0.05$) between the control group and valproic acid administered groups are represented by *.*

atherosclerosis by increasing endothelial permeability, lipoprotein retention in blood vessels, recruitment of inflammatory cells and the formation of foam cells" [8,13]. In our work, the administration of valproic acid resulted in disruption in cholesterol homeostasis in the blood. Valproic acid lowered total cholesterol in the plasma, increased HDL cholesterol and significantly lowered LDL+VLDL cholesterol. This finding is in agreement with previous studies [26-29]. HDL cholesterol is regarded as good cholesterol because it is protective by reversing cholesterol transport, inhibiting the oxidation of LDL-cholesterol by neutralizing the atherogenic effects of oxidized LDL-cholesterol. HDL-cholesterol helps to scavenge cholesterol from extrahepatic tissues in the presence of LCAT and brings it to the liver [30]. Increased HDL cholesterol may be due to increased LCAT activity which also contributes to the reduced cholesterol levels. A greater reduction of LDL cholesterol and VLDL cholesterol as observed in this study may lead to an increase in HDL cholesterol as there is a reciprocal relationship between the concentration of VLDL cholesterol and HDL cholesterol as observed in this study.

In the tissue, valproic acid intake significantly lowered brain cholesterol after 2 weeks of administration, however, cholesterol levels return to normal when valproic acid administration continues for 4 weeks. When the cholesterol level in the brain is reduced it affects the blood-brain barrier by reducing average fluidity and protein-free volume this makes the brain barrier becomes permeable to large molecules and ions. Thus, the autoregulatory mechanism for the backflush of cholesterol to the brain is enhanced, which can lead to hypercholesterolemia in the brain resulting in neurodegenerative diseases such as Alzheimer's disease [31]. Results of this study indicate that administration of valproic acid was associated with non-significant pulmonary and cardiac cholesterogenesis. Although the activity of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG CoA) reductase (the rate-limiting enzyme in cholesterol synthesis) was not determined in this study, the enhanced cholesterogenesis may be attributed to valproic acid-induced activation of HMG-CoA reductase or it may be due to feedback inhibition [32, 33]. "It may also be due to the inhibition of the activity of cholesterol-7α-hydroxylase, a cytochrome P450 enzyme located in the endoplasmic reticulum. This could limit the biosynthesis of bile acids, which is the only significant route for the elimination of cholesterol from the body" [34]. Since the liver has a limited capacity to store lipids, the excess cholesterol and triglycerides are packaged into VLDL particles and secreted into circulation. The effects of valproic acid administration on cholesterol levels of the liver, kidney and spleen are minimal and not significant suggesting that valproic acid has no adverse effect on cholesterol contents of these tissues although this observation may be different if a longer administration period of more than 4 weeks is used for the study.

Triacylglycerols, also called triglycerides are the most abundant dietary lipid compound which is used as storage fuel in the adipose tissue [35]. Administration of valproic acid significantly increased plasma, HDL, erythrocyte and LDL + VLDL triglyceride levels. "The key enzyme in the distribution of circulating lipids between organs is lipoprotein lipase (LPL), an enzyme located on the walls of blood capillaries" [36]. "The role of LPL in lipoprotein metabolism is well known. Since the majority of the circulating FFAs are present as triglycerides in lipoproteins, hydrolysis of this triglyceride by LPL is an important determinant of overall fatty acid uptake and ß-oxidation in the tissues" [37, 38]. Although the level of FFA was not determined in this study, it has been suggested that high circulating FFA can inhibit the activity of LPL [39]. Therefore, a significant reduction in the activity of LPL probably caused the accumulation of triglycerides in the plasma observed in this study.

"Several studies have shown a strong independent relation between plasma triglyceride levels and the likelihood of cardiovascular disease" [40,41]. "Proatherogenic metabolic or biochemical abnormalities often associated with elevated levels of triglycerides include decreased levels of HDL-C, increased FFAs, and increased TG-rich lipoproteins" [40,42]. Some of these proatherogenic metabolic abnormalities were observed in the present study, along with the hypertriglyceridemic condition. The induction of these abnormalities may be one possible mechanism by which valproic acid induces weight gain, dyslipidemia, blood dyscrasias, and liver injury as earlier reported by Nanau and Neuman, [7] and Belcastro et al., [8]. "Triglyceride-rich lipoproteins and their remnants may directly contribute to the formation of arterial-wall foam cells, as VLDL and intermediate-lipoproteins are known to be atherogenic" [43]. However, it must be stated that when the rats administered with valproic acid for 4 weeks in this study were allowed to recover for

7 days, the observed increased in triglyceride contents in the plasma, HDL and LDL+VLDL fractions were significantly reduced suggesting that the dyslipidaemia effect of valproic acid may be related to its prolonged use. Our study revealed that administration of valproic acid did not significantly affect the triglyceride content of the tissues and the few changes observed in the liver and brain can be said to be non-lipotoxic.

A phospholipid is a class of lipids that are a major component of all cell membranes as they can form a bilayer. They are organized into bilayer which serves as the framework in which the other components of the membrane are embedded [32]. “Changes in the level of phospholipids could compromise the integrity and function of cell membranes because they depend mainly on the lipid balance, especially on the cholesterol/phospholipid ratio” [44]. In this study, administration of valproic acid resulted in up-regulation of plasma and HDL phospholipid of the animals while its depleted LDL+VLDL and erythrocyte phospholipid levels. Elevation of phospholipid levels in the plasma and HDL may be a result of the stimulation of the endogenous phospholipid synthesis by valproic acid, through an over-expression of enzymes involved in the synthesis of phospholipids [45]. In addition, there might be an increase in the level of FFA which may result in high availability of fatty acids to form phospholipids.

“Administration of valproic acid did not result in tissue phospholipidosis in this study. Phospholipidosis is a lipid storage disorder in which abnormal quantities of phospholipids accumulate in various tissues” [33,46]. “Xenobiotic drugs and chemicals, as well as hormones, cofactors and other agents, may alter the metabolism of the cell and result in phospholipidosis” [33,46]. Valproic acid administration significantly lowered phospholipid levels in the heart and kidney while phospholipid levels in the liver, brain, lung and spleen were not significantly affected. Although the activity of phospholipase was not determined in this study, the lowered phospholipid level in the heart and kidney may not be unconnected with the enhancement of phospholipase by valproic acid which constantly degrades the phospholipid or inhibition of phospholipid biosynthesis due to the unavailability of FFA.

The effect of valproic acid on lipid profile is controversial [8] because several studies have found that valproic acid does not affect the lipid profile, while some studies have shown significant changes in lipid, lipoprotein and apolipoprotein profile due to valproic acid administration [8-11]. Our findings in this study revealed that valproic acid administration caused perturbations of major lipids in the animals, however, the perturbations did not significantly affect the lipid profile of the animals. The cholesterol was largely unaffected in most compartments except in the LDL+VLDL where it was significantly lowered. Although the triglycerides content of blood compartments was increased by valproic administration their levels drop significantly when rats were allowed to recover for 7 days. The tissue's triglyceride and phospholipid levels were unaffected by valproic acid administration. “Our finding is in total agreement with previous studies which conclude that administration of valproic acid for 1 year or more has no significant effect on triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol levels in adults” [28].

5. CONCLUSION

Although the argument on the effect of valproic acid administration on lipid profile still subsists, the result of our study is in support of the argument that valproic acid administration does not significantly affect lipid profile. The few cases of perturbation of lipid content observed in our study such as lowering of LDL+ VLDL cholesterol level, lowering of the brain and heart phospholipid content are non-lipotoxic.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All the ethical protocols laid by the committee in line with ARRIVE guidelines, and the national institutes of health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978) were followed.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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