The potential mechanisms of effect of valproic acid on lipid profiles: an updated review

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Received September 19, 2018
Accepted for publication October 31, 2018
Published on-line November 22, 2018

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Summary

Introduction. Valproic acid is commonly used for the treatment of epilepsy, psychiatric disorders such as bipolar disorders, anxiety and prophylaxis migraine. Long-term use of valproic acid is related with metabolic disorders such as the increase of body weight and changes of lipid profiles which are contributed to cardiovascular events, however, these associations remain unclear, furthermore, the mechanisms of these effects have not been fully elucidated.

Aim. To summarize and discuss the potential mechanisms of valproic acid-related changes of lipid profiles so as to get a better understanding of the side effects of valproic acid on lipid metabolism.

Methods. Literature reviews were conducted through the survey of the literature utilizing the Pubmed electronic databases, with the aim to identify all literature regarding the metabolic effects of valproic acid. This review has been written to summarize the latest evidence of valproic acid's effects on lipid profiles.

Review and Discussion. The possible mechanisms of valproic acid-related changes of lipid profiles could be through insulin resistance and hyperinsulinemia in several ways, resulting in the alteration of lipogenesis and clearance of triglyceride and lipoproteins.

Conclusion. The effect of valproic acid on lipid profiles is complex and there is a need for further investigation. Consequently the monitoring and follow up of lipid profiles from patients prescribed valproic acid is recommended.

Keywords: valproic acid • lipid profiles • side effects • epilepsy

INTRODUCTION

Valproic acid (2-propylpentanoic acid) is a branched-short-chain fatty acid derived from valeric acid which is extracted from Valeriana officinalis (Fan et al., 2016; Tomson et al., 2016). Valproic acid is commonly used for the treatment of epilepsy, psychiatric disorders such as bipolar disorder and anxiety and prophylaxis of a migraine (Ghodke-Puranik et al., 2013; Terbach and Williams, 2009; Tseng et al., 2017).

Valproic acid is well absorbed and has a very high ability to bind to albumin (87–95%), with the consequence being that there is a small part of valproic acid excreted by the kidneys (6–20 ml/day/kg body weight) (Silva et al., 2008). The plasma therapeutic levels of the long-term use of valproic acid are approximately 40–100 μg/ml or 280–700 μmol/L (Silva et al., 2008). Most of the valproic acid will be biotransformed endogenously through three mechanisms: 1) glucuronidation; 2) beta-oxidation in the mitochondria; and 3) P450 cytochrome-mediated oxidation (Ghodke-Puranik et al., 2013).

The side effects of valproic acid vary, and include sedation, fatigue, tremor, gastrointestinal symptoms,

and weight gain (Chen et al., 2014; Tomson et al., 2016). Long-term use of valproic acid 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 (Belcastro et al., 2013).

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 (Belcastro et al., 2013; Sakakura et al., 2013). Berenson et al. (1992) showed that there was a positive correlation between total cholesterol levels and atherosclerosis at a young age. Total cholesterol increases the risk of coronary heart disease by 2.52 (95% confidence interval: 1.15–5.07) in men and 3.20 (1.44–7.09) in women (Nagasawa et al., 2012). Epidemiological data show that there is an increase of the prevalence and death rates from atherosclerosis in adults with epilepsy (19% for all cases of epilepsy and 22,5% for idiopathic epilepsy) (Annegers et al., 1984).

The effect of valproic acid on lipid profiles is controversial (Belcastro et al., 2013). Several studies have found that valproic acid does not affect total cholesterol levels, as well as other lipid profiles (Belcastro et al., 2013; Luo et al., 2015; Płonka-Półtorak et al., 2016), while other studies have shown significant changes in lipid, lipoprotein and apolipoprotein profiles (Auley and Mooney, 2015; Belcastro et al., 2013; Erdemir et al., 2009; Luo et al., 2015). Regarding these circumstances, herewith we discuss the putative mechanisms of the effect of valproic acid on lipid profiles.

AIM

To summarize and discuss the potential mechanism of valproic acid-related changes of lipid profiles so as to get a better understanding of the side effects of valproic acid on lipid metabolism.

METHODS

Literature reviews were conducted through a search utilizing the Pubmed electronic databases www.ncbi.nlm.nih.gov/pubmed during June to July 2018, with the aim of identifying all literature regarding the metabolic effect of valproic acid using keywords such as valproate, metabolic syndrome, lipid profiles, lipoproteins, and cholesterol. This review has been written to summarize the latest evidence of valproic acid's effects in lipid profiles.

REVIEW AND DISCUSSION

Long-term use of valproic acid 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 (Belcastro et al., 2013).

The role of valproic acid in lipid profiles is controversial (Belcastro et al., 2013), and nowadays, there is no exact data regarding the putative mechanisms of these effects, even when it is clear that valproic acid has an effect on weight gain, which is observed during the first 3 months of therapy, reaching its maximum effect after 6 months. A long duration of therapy is associated with significant weight gain that continues after the first rapid increase in the first months of therapy. Although not all studies have analyzed the role of valproic acid dosage, literature has demonstrated that there an no correlations between the degree of weight gain and the daily valproic acid dosage and/or serum valproic acid concentration (Verrotti et al., 2009).

Abaci et al. (2009) demonstrated that valproic acid increases total cholesterol and low-density lipoprotein (LDL) cholesterol levels after 12 months of use, on the other hand, Wahyuni and Was'an (2013) reported that there was only a weak correlation between the duration of use of first-generation antiepileptic drugs (phenytoin, carbamazepine, and valproic acid) and total cholesterol levels and triglycerides ($r = 0.3$).

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 (Belcastro et al., 2013; Sakakura et al., 2013). Luo et al. (2015) demonstrated that the average carotid artery intima-media thickness (CA-IMT) of epileptic patients treated with valproic acid was higher than that of healthy people. This study provides evidence that valproic acid might contribute to the process of atherosclerosis.

The mechanism of lipid profile changes due to valproic acid is still unclear. A possible mechanism may be through the insulin resistance and hyperinsulinemia, resulting in impaired lipid transport and lipogenesis (Abaci et al., 2009).

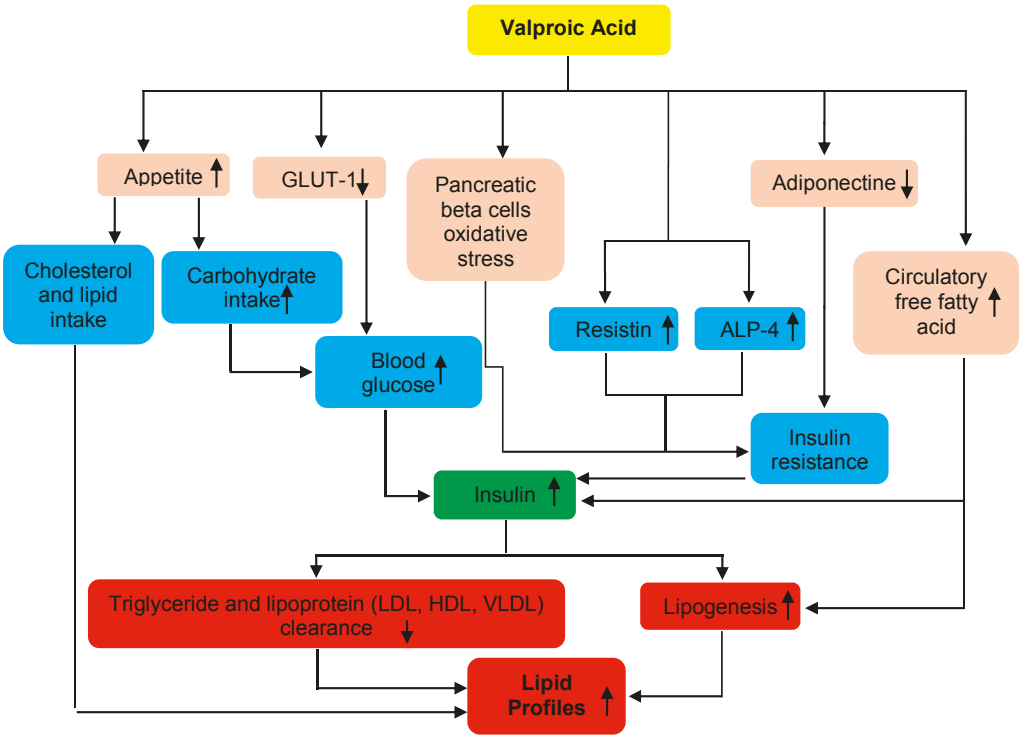

Figure 1. The putative mechanisms of valproic acid-related changes of lipid profiles (by Santoso Jaeri, unpublished data). GLUT-1 – Glucose Transporter-1; LDL – Low Density Lipoprotein; ALP-4 – Angiopoetin-Like Protein-4; HDL – High Density Lipoprotein; VLDL – Very Low Density Lipoprotein.

Insulin is a peptide hormone secreted by pancreatic beta cells that control the synthesis and storage of lipids in the liver. Insulin increases de novo lipogenesis, esterification and triglyceride secretion in the liver. Additionally, it also inhibits fatty acid oxidation and lipolysis (Titchenell et al., 2017). Insulin inhibits lipolysis in the adipocytes by activating the phosphoinositol-3-kinase signal which provides catecholamine inhibitory effects in the lipolysis, resulting in reduced levels of free fatty acids and glycerol in the circulation (Belcastro et al., 2013). Insulin plays a role in the process of triglyceride clearance through lipoprotein lipase (LPL) activation and triglyceride output through its effect on synthesis and secretion of very low-density lipoprotein (VLDL) in the liver.

Valproic acid causes hyperinsulinemia in several ways (Figure 1). Valproic acid causes hyperinsulinemia and insulin resistance by affecting several organs or tissues, such as adipose tissue, hypothalamus, pituitary and pancreatic beta cells (Belcastro et al., 2013).

The use of valproic acid causes hypothalamic dysregulation due to an increase in gamma-aminobutyric acid (GABA) transmission in the hypothalamic axis, which results in an increase of appetite with a consequences being the increase of cholesterol and carbohydrate intake (Verrotti et al., 2009). Egger and Brett (1981) reported that there was weight gain in 44 of the 100 children treated with valproic acid. Increased appetite and excessive weight gain also were reported in 31 of 66 patients with generalized epilepsy and 13 of 34 with partial epilepsy treated with valproic acid. These numbers were significantly increased within a year after valproic acid treatment (37.5%) compared to other antiepileptic drugs (10%) (Egger and Brett, 1981). The composition of lipids in the liver is derived from food (15%), de novo synthesis (30%), and adipose tissues (60%) (Sozio et al., 2010).

The effect of dietary cholesterols on plasma cholesterol levels is still controversial. Several studies have shown that dietary cholesterols increase LDL cholesterol levels. (Auley and Mooney, 2015). Other studies reported that dietary cholesterols have a minimal effect on plasma cholesterol levels. On the other hand, a meta-analysis showed that dietary cholesterols do not affect plasma cholesterol levels (Alphonse et al., 2017).

High carbohydrate intake can increase blood glucose

levels resulting in an elevated level of insulin. This phenomenon will cause the conversion of carbohydrates to triglycerides through the breakdown of acetyl Co-A in the cycle of fatty acid synthesis (Sozio et al., 2010).

Valproic acid increases the expression of resistin and a fasting-induced adipose factor known as angiopoietin-like protein-4 (ALP-4). Both proteins contribute to insulin resistance (Belcastro et al., 2013).

Resistin is a member of the resistin-like molecule (RELM) family of cysteine-rich proteins. Resistin is secreted in the form of trimers or hexamers by adipocytes in rodents and monocytes/macrophages in humans (Wang et al., 2017). In addition, resistin is also produced in the ventromedial nucleus, and hippocampus (Bacloer et al., 2015). The structure of resistin molecule in humans is a polypeptide with a molecular weight of 10-kDa. Resistin contains 108 amino acids with 16 peptide signal residues (Park et al., 2017). The role of resistin in the pathogenesis of obesity-mediated insulin resistance and type 2 diabetes is still unclear. In rodents, it has been shown that resistin causes severe hepatic insulin resistance through several ways such as increasing the expression of pro-inflammatory cytokines, inhibiting the 5' adenosine monophosphate-activated protein kinase (AMPK) phosphorylation and inducing the suppressor of cytokine signaling 3 (SOCS3) (Huang and Yang, 2016). Resistin also reduces gene expression encoding for hepatic gluconeogenesis enzymes (Antuna-Puentea et al., 2008).

Angiopoietin-like protein-4 (ALP-4) is one of the angiopoietin-like proteins that play a role in the homeostasis of lipid and glucose metabolism (Li and Teng, 2014). ALP-4 has a molecular weight of 45–65 kDa. ALP-4 is composed of glycoproteins and 406 amino acids. An increase in the expression of ALP-4 causes an increase in triglyceride and cholesterol levels (Grootaert et al., 2012).

Valproic acid also has an effect on other adipokines released by the adipose tissue such as adiponectin, leptin, leptin receptors and ghrelin (Verrotti et al., 2009). Adiponectin has a role in regulating the metabolism of glucose and lipids (Huang and Yang, 2016). Adiponectin decreases the gluconeogenesis process to prevent hyperglycemia (Li et al., 2013). Valproic acid inhibits adiponectin expression through the inhibition of histone deacetylases (HDAC) resulting in an increased gluconeogenesis process. The suppression of these expressions causes an increase of fatty acid oxidation and insulin resistance associated with valproic acid (Belcastro et al., 2013).

Valproic acid is a branched short-chain fatty acid. It has a high affinity to albumin, competing with free fatty acids to bind to albumin hence causing an increase in free fatty acid levels. Increased availability of free fatty acids in the blood, in turn, modulates insulin secretion (Verrotti et al., 2009).

Valproic acid also affects directly the pancreatic beta cells to secrete insulin, resulting in an inappropriate level of insulin. The mechanism of secretion of insulin by beta cells is complex and dependent on many factors. Valproic acid increases the oxidative stress state of beta cells resulting in its dysfunction. Beta cells are sensitive to reactive oxygen species (ROS) and reactive nitrogen species (RNS) because they are low in free-radical quenching (antioxidant) enzymes such as catalase, glutathione peroxidase, and superoxide dismutase. Oxidative stress in the beta cells has the ability to damage mitochondria, which impairs the impaired the mitochondrial processes involved in glucose-mediated insulin secretion (Evans et al., 2003).

Hyperinsulinemia by valproic acid also results from the effects of valproic acid on insulin-mediated intracellular glucose transport. Intracellular glucose transport is assisted by five glucose-carrying proteins, one of which is Glucose transporter-1 (GLUT-1). GLUT-1 is an integral membrane protein that is present in most of the boundaries between blood vessels and tissues. It plays a role in the basal energy supply of the network. The conformational model of GLUT-1 is composed of the 12 α-helical transmembrane segments, the amino and carboxy intracellular terminals, the intracellular loop, and the extracellular loop consisting of the N-glycosylation site (Klepper and Voit, 2002). Valproic acid can inhibit GLUT-1 activity, thereby reducing intracellular glucose transport and decreasing the expression of GLUT-1 mRNA. A decrease in intracellular glucose transport causes an increase in blood glucose levels that can stimulate insulin secretion (Verrotti et al., 2009).

CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, although the relationship between valproic acid and GABA action is generally accepted, the relationship between valproic acid and lipid profile changes have not been fully elucidated. There are potential complex mechanisms of valproic acid on lipid profiles. In order to determine the exact molecular aspects of the fundamental physiological mechanisms of these events, further studies are needed. There are several challenges such as identifying the genes which are

responsible for these effects. In further studies, the use of models such as experimental animals might be necessary since there are many confounding factors when the studies were carried out on human subjects. Another issue is that because there are an increase of dyslipidemia cases on a patient using valproic acid, the monitoring and follow up of lipid profiles from patients prescribed valproic acid should be considered.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

REFERENCES

Abaci A., Saygi M., Yis U., Demir K., Dirik E., Bober E.: *Metabolic alterations during valproic acid treatment: a prospective study*. Pediatr. Neurol., 2009, 41: 435–439. doi: 10.1016/j.pediatrneurol.2009.06.00.

Alphonse P.A.S., Ramprasath V., Jones P.J.H.: *Effect of dietary cholesterol and plant sterol consumption on plasma lipid responsiveness and cholesterol trafficking in healthy individuals*. British Journal of Nutrition, 2017, 117: 56–66. doi: 10.1017/S0007114516004530.

Annegers J.F., Hauser W.A., Shirts S.B.: *Heart disease mortality and morbidity in patients with epilepsy*. Epilepsia, 1984, 25: 699–704.

Antuna-Puentea B., Feve B., Fellahi S., Bastard J.P.: *Adipokines: The missing link between insulin resistance and obesity*. Diabetes & Metabolism, 2008, 34: 2–11. doi:10.1016/j.diabet.2007.09.004.

Auley M.T.M., Mooney K.M.: *Computationally Modelling Lipid Metabolism and Aging: A Mini-review*. Computational and Structural Biotechnology Journal, 2015, 13, 38–46. doi: 10.1016/j.csbj.2014.11.006.

Bacloer E., Kosari S., Stebbing M.J.: *Resistin, an adipokine with non-generalized actions on sympathetic nerve activity*. Frontier in Physiology, 2015, 6: 321. doi: 10.3389/fphys.2015.00321.

Belcastro V., D'Egidio C., Striano P., Verrotti A.: *Metabolic and endocrine effects of valproic acid chronic treatment*. Epilepsy Research, 2013, 107: 1–8. doi: 10.1016/j.eplepsyres.2013.08.016.

Berenson G.S., Wattigney W.A., Tracy R.E., Newman W.P. 3rd, Srinivasan S.R., Webber L.S. et al.: *Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (The Bogalusa Heart Study)*. Am. J. Cardiol., 1992, 70: 851–858.

Chen S., Wu H., Klebe D., Hong Y., Zhang J.: *Valproic acid: a new candidate of therapeutic application for the acute central nervous system injuries*. Neurochem. Res., 2014, 39: 1621–1633. doi: 10.1007/s11064-014-1241-2.

Egger J., Brett E.M.: *Effects of sodium valproate in 100 children with special reference to weight*. Br. Med. J., (Clin. Res. Ed.), 1981, 283: 577–581.

Erdemir A., Cullu N., Yis U., Demircioglu F., Kir M., Cakmakci H. et al.: *Evaluation of serum lipids and carotid artery intima media thickness in epileptic children treated with valproic acid*. Brain & Development, 2009, 31: 713–716. doi: 10.1016/j.braindev.2008.11.001.

Evans J.L., Goldfine I.D., Maddux B.A., Grodsky G.M.: *Are oxidative stres-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction*? Diabetes, 2003, 52: 1–8. doi: 10.2337/diabetes.52.1.1.

Fan H.C., Lee H.S., Chang K.P., Lee Y.Y., Lai H.C., Hung P.L.: *The impact of anti-epileptic drugs on growth and bone metabolism*. Internat Journal of Molecular Sciences, 2016, 17: 1–22. doi:10.3390/ijms17081242.

Ghodke-Puranik Y., Thorn C.F., Lamba J.K., Leeder J.S., Song W., Birnbaum A.K. et al.: *Valproic acid pathway: pharmacokinetics and pharmacodynamics*. Pharmacogenet Genomics, 2013, 23: 236–241. doi: 10.1097/FPC.0b013e32835ea0b2.

Grootaert C., Van der Wiele T., Verstraete W., Bracke M., Vanhoecke B.: *Angiopoietin-like protein 4: health effects, modulating agents and structure-function relationship*. Expert Review of Proteomics, 2012, 9: 181–199. doi:10.1586/epr.12.12.

Huang X., Yang Z.: *Resistin's, obesity, and insulin resistance: the continuing disconnect between rodents and humans*. J. Endocrinol. Invest., 2016, 39: 607–615. doi: 10.1007/s40618-015-0408-2.

Klepper J., Voit T.: *Facilitated glucose transporter protein type 1 (GLUT1) deficiency syndrome: impaired glucose transport into brain – a review*. Eur. J. Pediatr., 2002, 161: 295–304. doi: 10.1007/s00431-002-0939-3.

Li Y., Ding L., Hassan W., Abdelkader D., Shang J.: *Adipokines and hepatic insulin resistance*. Journal of Diabetes Research, 2013, Article ID 170532. doi: 10.1155/2013/170532.

Li Y., Teng C.: *Angiopoetin-like proteins 3, 4, and 8: regulating lipid metabolism and providing new hope for metabolic syndrome*. Journal of Drug Targeting, 2014, 22: 679–687. doi: 10.3109/1061186X.2014.928715.

Luo X., Zhang M., Deng L., Zhao J.: *Effects of valproate on the carotid artery intima-media thickness in epileptics*. Indian Journal of Pharmacology, 2015, 47: 45–48. doi: 10.4103/0253-7613.150328.

Nagasawa S.Y., Okamura T., Iso H., Tamakoshi A., Yamada M., Watanabe M. et al.: *Relation between serum total cholesterol level and cardiovascular disease stratified by sex and age group: a pooled analysis of 65 594 individuals from 10 cohort studies in Japan*. J. Am. Heart Assoc., 2012, 1: e001974. doi: 10.1161/JAHA.112.001974.

Park H.K., Kwak M.K., Kim H.J., Ahima R.S.: *Linking resis-*

tin, inflammation and cardiometabolic diseases. Korean J. Intern. Med., 2017, 32: 239–247. doi: 10.3904/kjim.2016.229.

Płonka-Półtorak E., Zagrodzki P., Kryczyk-Kozioł J., Westermarck T., Kaipainen P., Kaski M., Atroshi F.: *Does valproate therapy in epileptic patients contribute to changing atherosclerosis risk factors? The role of lipids and free fatty acids*. Pharmacological Reports, 2016, 68: 1339–1344. doi: 10.1016/j.pharep.2016.09.001.

Sakakura K., Nakano M., Otsuka F., Ladich E., Kolodgie F.D., Virmani R.: *Pathophysiology of atherosclerosis plaque progression*. Heart, Lung, and Circulation, 2013, 22: 399–411. doi: 10.1016/j.hlc.2013.03.001.

Silva M.F., Aires C.C., Luis P.B., Ruiter J.P., Jist L.I., Duran M. et al.: *Valproic acid metabolism and its effects on mitochondrial fatty acid oxidation: a review*. J. Inherit. Metab. Dis., 2008, 31: 205–216. doi: 10.1007/s10545-008-0841-x.

Sozio M.S., Liangpunsakul S., Crabb D.: *The role of lipid metabolism in the pathogenesis of alcoholic and nonalcoholic hepatic steatosis*. Seminars in Liver Disease, 2010, 30: 378–390. doi: 10.1055/s-0030-1267538.

Terbach N., Williams R.S.: *Structure-function studies for the panacea, valproic acid*. Biochemical Society Transaction, 2009, 37: 1126–1132. doi: 10.1042/BST0371126.

Titchenell P.M., Lazar M.A., Birnbaum M.J.: *Unraveling the regulation of hepatic metabolism by insulin*. Trends in Endocrinology & Metabolism, 2017, 28: 497–505. doi: 10.1016/j.tem.2017.03.003.

Tomson T., Battino D., Perucca E.: *Valproic acid after five decades of use in epilepsy: time to reconsider the indications of time-honoured drug*. Lancet Neurol., 2016, 15: 210–218. doi: 10.1016/S1474-4422(15)00314-2.

Tseng J.H., Chen C.Y., Chen P.C., Hsiao S.H., Fan C.C., Liang Y.C., Chen C.P.: *Valproic acid inhibits glioblastoma multiforme cell growth via paraoxonase 2 expression*. Oncotarget, 2017, 8: 14666-14679. doi: 10.18632/oncotarget.14716.

Verrotti A., Torre R.L., Trotta D., Mohn A., Chiarelli F.: *Valproate-induced insulin resistance and obesity in children*. Horm. Res., 2009, 71: 125–131.

Wahyuni K.D., Was'an M.: *Korelasi antara Durasi Terapi Obat Antiepilepsi Generasi Pertama dengan Kadar Profil Lipid pada Penyandang Epilepsi Idiopatik*. Postgraduate Thesis, Universitas Gajah Mada, 2013, Yogyakarta Indonesia.

Wang Y., Ma X.L., Lau W.B.: *Cardiovascular adiponectin resistance: the critical role of adiponectin receptor modification*. Trends in Endocrinology & Metabolism, 2017, 28: 519–530. doi: 10.1016/j.tem.2017.03.004.