



REVIEW

Metabolic and endocrine effects of valproic acid chronic treatment

Vincenzo Belcastro^{a,*}, Claudia D'Egidio^b, Pasquale Striano^c,
Alberto Verrotti^d

^a Neurology Unit, Department of Neuroscience, Sant'Anna Hospital, Como, Italy

^b Department of Pediatrics, University of Chieti, Chieti, Italy

^c Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, "G. Gaslini" Institute, Genova, Italy

^d Department of Pediatrics, University of Perugia, Perugia, Italy

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Summary Treatment of epileptic patients with valproic acid (VPA) may be associated with substantial weight changes that may increase morbidity and impair adherence to the treatment regimen. VPA-induced weight gain seems to be associated with many metabolic disturbances; the most frequent are hyperinsulinemia and insulin resistance, hyperleptinemia and leptin resistance. Patients who gain weight during VPA therapy can develop dyslipidemia and metabolic syndrome that are associated with long-term vascular complications such as hypertension and atherosclerosis. Moreover, an elevation in the levels of uric acid and homocysteine, together with oxidative stress, may contribute to atherosclerotic risk in patients under long-term therapy with VPA.

The aim of this review is to discuss the metabolic and endocrine effects of VPA chronic treatment in patients with epilepsy.

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* Corresponding author. Tel.: +39 0 31 5859682; fax: +39 0 31 5859684.

E-mail addresses: vincenzobelcastro@libero.it, belcastrov76@gmail.com (V. Belcastro).

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Introduction

Anticonvulsant properties of valproic acid (VPA), which is structurally unrelated to other antiepileptic drugs, were discovered by chance. The drug was first synthesized in 1882 by [Burton \(1882\)](#) as an analogue of valeric acid, naturally found in valerian ([Burton, 1882](#)). VPA is a fatty acid that is a clear liquid at room temperature and, for many decades, its only use was in laboratories as a solvent for organic compounds. In 1962, Pierre Eymard, a research student at the University of Lyon, used VPA as a solvent to investigate the potential anticonvulsant drugs with low aqueous solubility against pentylenetetrazol-induced convulsions (PTZ) in laboratory rats. A strong anticonvulsant activity was observed in all solutions where the compound was present, leading to investigate VPA as a potentially useful agent for epilepsy ([Meunier et al., 1963](#)). Thus, VPA was approved as an antiepileptic drug in 1967 in France and it is currently the antiepileptic drug (AED) with the broadest spectrum across all types of seizures and epileptic syndromes ([Aldenkamp et al., 2006](#); [Striano and Belcastro, 2012, 2013](#)). Further, VPA was the first, and, until the 1990, the only drug with a very broad spectrum of activity and its efficacy has been seen in idiopathic generalized epilepsy with or without photosensitivity, idiopathic focal and symptomatic generalized tonic-clonic seizures ([Aldenkamp et al., 2006](#)). In addition, VPA has gained acceptance in the treatment of bipolar disorder and impulsive–aggressive behaviour in patients with personality disorders other than in migraine prophylaxis ([Johannessen Landmark, 2008](#)).

While the side effects of VPA are well documented in clinical practice, little is known about the effects of chronic VPA treatment. Given the heterogeneous prescribing patterns and varied benefits of VPA, the clarification of their safety profile merits attention. VPA has been associated with metabolic and endocrine disorders as weight gain and hyperinsulinaemia that may contribute to cardiovascular risk in patients with epilepsy ([Verrotti et al., 2010](#)). Moreover, possibly influencing atherothrombotic risk factors such as serum lipids, lipoprotein (a), uric acid level and homocysteine, VPA treatment may represent an underlying risk factor for systemic vascular diseases.

Despite its long-standing usage, the mechanism (s) of the anticonvulsant activity of VPA is still controversial. In fact, mechanistic studies originally focused on its ability to dampen neuronal hyperexcitability by potentiation of inhibitory neurotransmission through an effect on γ -aminobutyric acid (GABA) metabolism, while more recent studies have shown new activities for VPA including effects on voltage-gated sodium channels, NMDA receptor-mediated actions and as Histone deacetylase (HDAC) inhibitor.

This article reviews on the effects of VPA chronic treatment, focusing on metabolic and endocrine disorders and as possible risk factor for atherosclerosis.

Valproic acid and weight gain

Significant weight gain has been one of the most frequently experienced problems in patients with epilepsy (10–70%) spanning paediatric to adult usage of VPA ([Isojärvi et al., 1996](#); [Novak et al., 1999](#); [Rättyä et al., 1999](#); [Verrotti et al., 1999, 2002, 2004, 2010](#); [Pylvänen et al., 2002](#); [El-Khayat et al., 2004](#); [de Vries et al., 2007](#); [El-Khatib et al., 2007](#); [Hamed et al., 2009](#); [Sharpe et al., 2009](#)).

Among all these studies, weight change has not been evaluated specifically in VPA clinical trials except in a double-blind, 1 year study of new onset seizures comparing CBZ, topiramate, and VPA ([Privitera et al., 2003](#)). In this study, patients receiving VPA increased their weight by an average of 2.0 kg (2.8% of baseline weight) and 5.0 kg in children. Conversely, CBZ was weight neutral ([Privitera et al., 2003](#)). In a double-blind study comparing lamotrigine (LTG) and VPA, weight changes were assessed and after 32 weeks of treatment, mean weight gain was significantly higher in VPA-treated than LTG-treated patients ([Biton et al., 2003](#)).

With regard to the potential risk factors, results from clinical studies have suggested that the occurrence of weight gain is more prevalent in females with epilepsy than in males ([Stephen et al., 2001](#); [Hamed et al., 2009](#); [Kanemura et al., 2012](#)), therefore, the gender may be considered one of risk factors for VPA-induced weight gain. In particular, [El-Khatib et al. \(2007\)](#) reported a significant weight gain in 43.6% of women compared with 23.5% of men receiving VPA therapy. Furthermore, percentage of body fat and waist-to-hip ratio differed statistically between genders with women having higher percentage of body fat and a lower waist/hip ratio.

From the analysis of these data, in female patients, a further risk factor is the younger age: the increase in body weight appears to occur more frequently in post pubertal girls taking VPA ([Rättyä et al., 1999](#); [Verrotti et al., 1999](#); [Biton et al., 2003](#); [Prabhakar et al., 2007](#); [de Vries et al., 2007](#)) and body weight increase is more common in patients treated with VPA during puberty if epilepsy and therapy continue into adulthood ([Mikkonen et al., 2005](#)). In adolescent girls, excessive weight gain has not only serious psychological effects but can also causes the development of important endocrinological abnormalities and a decrease of treatment compliance. Then, this side effect must be addressed if medication for females with epilepsy is begun before 20 years of age. The mechanism through which VPA may induce a weight gain is matter of discussion. However, various hypotheses have been submitted to explain the effect of VPA on weight increase: dysregulation of the hypothalamic system, effect on adipokine levels, hyperinsulinaemia, IR. Experimental data have demonstrated that VPA can cause dysregulation of the hypothalamic system ([Lakhanpal and Kau, 2007](#)). This theory may be explained by the enhancement of GABA transmission within the hypothalamic axis ([Biton et al., 2003](#)) and it is supported

by the observation that VPA-treated epileptic patients who reported weight gain developed increased appetite and quenching with calorie-rich beverages (Verrotti et al., 1999). A more recent hypothesis is that VPA may induce weight gain by the modifying expression of adipokine genes that are expressed in the brain and pituitary (cephalokines); these genes codify for neuropeptides involved in central energy metabolism, such as resistin and fasting-induced adipose factor also known as angiopoietin-like protein 4, which have become major targets implicated in the aetiology of obesity and development of leptin and insulin resistance (IR) (Brown et al., 2008). Although VPA may modify hypothalamic gene expression in vitro (Münzberg and Myers, 2005), it is unclear whether it has similar effects in vivo.

VPA may have effects on adipokine released by adipose tissue, such as adiponectin, leptin, soluble leptin receptor and on ghrelin. Ghrelin is the natural ligand of the growth hormone secretagogue receptor. In fact, VPA can suppress adiponectin gene expression in adipocytes through HDAC inhibition (Qiao et al., 2006). These findings are in agreement with data showing lower concentrations of adiponectin in patients with obesity and type 2 Diabetes, providing a clear evidence of a relationship between overweight and overweight-related disorders (Greco et al., 2005). Interestingly, VPA can increase the expression of mRNA of adiponectin-binding receptors, adipoR1, in human hepatoma cell line HepG2 cells (Rauchenzauner et al., 2008a). As adiponectin mRNA expression is known to be downregulated following VPA treatment in vivo (Greco et al., 2005) and in vitro (Qiao et al., 2006), increased adipoR1 mRNA expression in liver cells possibly represents a favoured reaction balancing suppressed adiponectin secretion from adipocytes; changes in this balance of receptor/ligand expression might contribute to changes in fatty acid oxidation and IR in VPA-related obesity.

On the other side, hyperleptinaemia and leptin resistance are associated with obesity; consequently, this condition can explain the VPA-induced weight gain: clinical studies reported increased serum levels of leptin in children and adults who gain weight during VPA treatment (Aydin et al., 2005; Hamed et al., 2009; Rauchenzauner et al., 2008b). The effects of VPA on leptin biology and fatty acid metabolism have been tested in 3T3-L1 adipocytes (Rauchenzauner et al., 2008c): in vitro, VPA paradoxically reduces leptin mRNA levels and secretion of the leptin protein in a dose- and time-dependent manner. Probably, the inhibition of leptin secretion by VPA induces enhanced appetite in patients, resulting in enhanced adiposity and an increase in leptin secretion (see Fig. 1; Table 1).

Finally, because an association between ghrelin levels and obesity has been shown in humans (ghrelin levels are reduced in obesity), several studies have studied the relationship between VPA treatment and ghrelin: it seems that ghrelin levels are reduced in VPA-induced obesity (van der Lely et al., 2004; Greco et al., 2005; Ness-Abramof and Apovian, 2005; Gungor et al., 2007; Prodam et al., 2012). It is known that ghrelin influences glucose and insulin metabolism and the control of food and energy intake through the neuropeptide Y (NPY) system. Furthermore, ghrelin levels are reduced in obesity (van der Lely et al., 2004). Interestingly, Prodam et al. (2012) showed that ghrelin levels are decreased in very young prepubertal

children prior to and independent of a consistent weight gain during the first years of VPA: so, a derangement in ghrelin secretion in epilepsy during VPA treatment and independent of weight gain could be hypothesized.

Valproic acid and hyperinsulinaemia

In general, hyperinsulinaemia is known to be associated with obesity, dyslipidaemia and IR. Several studies in adults and children have established that hyperinsulinemia occurs in patients treated with VPA after the increase of body weight (Rättäjä et al., 1999; Verrotti et al., 1999; Stephen et al., 2001; Luef et al., 2002a,b; Pylvänen et al., 2002; Verrotti et al., 2002; El-Khayat et al., 2004; Pylvänen et al., 2006; Hamed et al., 2009; Kanemura et al., 2012).

Thus, it is likely that the VPA-induced weight gain is the cause of hyperinsulinemia and IR (Verrotti et al., 2010) and, consequently, patients who gain weight and develop IR after VPA treatment may have a higher risk of metabolic MS than patients without an increase of the body weight. On the other hand, Isojärvi et al. firstly found that the development of hyperinsulinemia and IR in long-term VPA therapy may be among multiple factors leading to weight gain in some patients. This observation is in agreement with data of successive studies that have suggested that hyperinsulinaemia in obese patients taking VPA is not merely a consequence of IR induced by weight gain but the development of IR may be one of the factors leading to weight gain in some patients (Pylvänen et al., 2002; Verrotti et al., 2002; Pylvänen et al., 2003; Lihn et al., 2005; Pylvänen et al., 2006). This is supported by the observation that weight gain during VPA treatment is related to increase in insulin concurrent with decrease in glucose level, which can stimulate appetite and may cause weight gain (Demir and Aysun, 2000). Interestingly, Pylvänen et al. (2006) have tried to explain as VPA may also determine hyperinsulinaemia in lean patients: they studied 51 adult patients on VPA monotherapy and compared them with 45 healthy control subjects with respect to fasting plasma glucose, serum insulin, proinsulin and C-peptide concentrations after overnight fast. The VPA-treated patients had fasting hyperinsulinaemia, although the fasting serum proinsulin and C-peptide concentrations were not significantly higher compared with the control. Therefore, VPA could not induce insulin secretion but may interfere with insulin metabolism in the liver, resulting in higher insulin concentrations in peripheral circulation. With regard to the mechanisms by which VPA may induce IR, other hypotheses have been proposed such as the increased plasma levels of free fatty acids (FFA) caused by VPA (McGarry, 2002; Luef et al., 2002a,b), b-cell dysfunction as a consequence of the oxidative stress (Evans et al., 2003), a direct effect on b-cells regulation and insulin secretion (Luef et al., 2009), and finally, an alteration of the sympathetic nervous system by acting on hypothalamic neurons (Breum et al., 1992). Recently, retinol-binding protein 4 (RBP4) and Glucagon-like peptide-1 (GLP-1) are considered as important new targets in modern type 2 diabetes mellitus therapy linked to IR and nonalcoholic fatty liver disease (NAFLD); Rauchenzauner et al. (2012) have demonstrated the lack of an influence of VPA treatment on RBP4 and GLP-1 in otherwise healthy patients. In summary, the absence of any relationship with

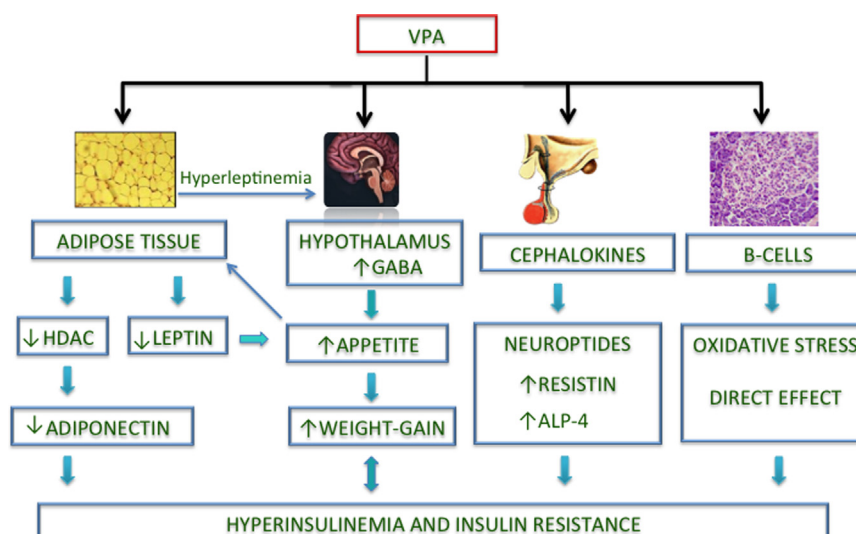


Fig. 1 Pathogenetic mechanisms of VPA-induced weight.

VPA: valproic acid; ALP-4: angiopoietin-like protein.

RBP4 and GLP-1 concentrations does not suggest a role of these novel IR parameters as potential regulators of glucose and fat metabolism during VPA-therapy.

Valproic acid and metabolic syndrome

Metabolic syndrome (MS) is a constellation of metabolic risk factors that includes increased waist circumference, atherogenic dyslipidemia, elevated blood pressure, and elevated blood glucose associated with IR (Alberti et al., 2006). Several meta-analyses have shown that MS is associated with an approximately 2-fold increased risk of cardiovascular disease (Isomaa et al., 2001; Lakka et al., 2002; Mottillo et al., 2010).

Recent studies have revealed that MS represents an enormous economic burden and is considered a serious public health problem (Fu et al., 2007; Wang et al., 2010). High prevalence of MS has been reported among patients with bipolar disorder who experienced significant weight gain associated with VPA (de Almeida et al., 2012). However, the presence of MS among obese patients with epilepsy on VPA has received little attention. We have conducted a

prospective study that focused on VPA-treated children and adolescents; our study showed that 40.4% of the patients exhibited considerably body weight, whereas 43.5% of the obese patients were diagnosed with MS at the end of the 24 months of follow-up (Verrotti et al., 2010). A study evaluating the presence of MS among Chinese adult obese patients with epilepsy on VPA therapy suggests that obese patients with epilepsy treated with VPA are at higher risk of MS than individuals who are simply obese (Fang et al., 2012); this study also demonstrated the homeostatic model assessment (HOMA) index is related to MS development rather than body-mass index. Thus, the HOMA index should be monitored in obese VPA-treated patients routinely (Fang et al., 2012). In addition, the possible relevant factors for MS development among patients were determined: MS was associated with high VPA doses but was independent of age, gender, seizure type, and duration of medication. This finding has to be considered an important matter, as the necessary dosage might be adjusted to minimize the possibility of occurrence of MS attributed to VPA treatment.

In the last years, it has been demonstrated that IR may be related to the development of non-alcoholic fatty liver disease (NAFLD) (Angulo, 2002). NAFLD can be considered a

Table 1 Summary of the potential metabolic and endocrine effects of valproic acid chronic treatment.

Effect	Risk factor	Mechanism
Weight gain	Female, young age	Dysregulation of the hypothalamic system, effect on adipokine levels, hyperinsulinaemia
Hyperinsulinaemia	VPA-induced weight gain	VPA interferes with insulin metabolism in the liver
Insulin resistance	VPA-induced weight gain	Increased plasma levels of FFA, b-cell dysfunction increased insulin secretion
Metabolic syndrome	High VPA doses	IR, NAFLD
Atherogenesis	Dyslipidemia, hyper-Hcy high uric acid level gain.	Dysfunction of the vessel wall

IR: insulin resistance; VPA: valproic acid; FFA: free fatty acids; NAFLD: non-alcoholic fatty liver disease; Hcy: homocysteine.

feature of the metabolic syndrome (Marchesini et al., 2001), associated with the presence of IR. In three clinical studies (Stierner, 1989; Luef et al., 2004, 2009), ultrasound examination of the liver in patients affected by epilepsy revealed that 61% of patients on VPA and 21% with CBZ had NAFLD. However, taking into account that NAFLD may be dangerous because it can be considered a component of the MS and it can be followed by cirrhosis, an early diagnosis is essential.

Valproic acid and atherogenesis

Atherosclerosis is the leading cause of death in the developed world, although its true frequency is difficult to be accurately determined because it is a predominantly asymptomatic condition (Berenson et al., 1998). Interestingly, epidemiological studies have indicated that the prevalence and death rates from atherosclerosis related cardiovascular disease are elevated in adult epileptic patients (Annegers et al., 1984; Gaitatzis et al., 2004). Influence of AEDs on the development of atherosclerosis has been the subject of controversy; in fact, recent evidence indicates that prolonged antiepileptic treatment might modify some vascular risk factors (Hamed and Nabeshima, 2005; Hamed et al., 2007; Elliott et al., 2007) while other studies showed that the mortality due to ischaemic heart disease appears to be lower in treated epileptics than in the general population (Kaste et al., 1983; Muuronen et al., 1985; Olesen et al., 2011). Recent studies have provided evidence that chronic administration of older AEDs is associated with the undesirable metabolic side effects (Mintzer and Mattson, 2009; Brodie et al., 2013) implicated in dysfunction of the vessel wall (Tan et al., 2009), the key pathophysiological mechanism promoting atherosclerosis.

It is well established that an increased carotid artery intima media thickness (CA-IMT) is a good predictor of clinical manifestation of atherosclerosis (Polak et al., 2011). Noteworthy, several studies of carotid arteries in patients with epilepsy have demonstrated significantly increased CA-IMT relative to normal controls (Hamed et al., 2007; Tan et al., 2009; Chuang et al., 2012). Interestingly, Erdemir et al. (2009) found an increased CA-IMT in epileptic children treated with VPA, while in a similar manner, the authors failed to find an increased CA-IMT in epileptic children treated with oxcarbazepine (Yiş and Doğan, 2012).

The first signs of hyperlipidemia can be detected in childhood (Strong et al., 2001), and fatty streaks, which are the earliest pathologic lesions of the atherogenic process, can be observed in the arteries of individuals by the age of 20 years (Berenson et al., 1998). Dyslipidemia has long been known to be an important risk factor for atherosclerosis (Kullo and Ballantyne, 2005). Low density lipoproteins (LDLs) plays an important role in the atherosclerotic process by increasing endothelial permeability, retention of lipoproteins within the intima of blood vessels, recruitment of inflammatory cells and formation of foam cells (Stocker and Keaney, 2004; Kullo and Ballantyne, 2005). Emerging evidence showed that treatment with enzyme-inducing AEDs, such as carbamazepine (CBZ) and phenytoin (PHT) is significantly associated with increased blood levels of total cholesterol, atherogenic (non-HDL) cholesterol and

triglycerides. Probably, the increase in thickness of CCA IMT in patients treated with PHT or CBZ may be related to total cholesterol and LDLs (Chuang et al., 2012; Sonmez et al., 2006; Tomoum et al., 2008). Instead, the effects of VPA on changes in lipid profiles and lipoproteins remains controversial (Eiris et al., 1995; Geda et al., 2002; Nikolaos et al., 2004; Pylvänen et al., 2006; Abaci et al., 2009; Grosso et al., 2009; Lopinto-Khoury and Mintzer, 2010; Chuang et al., 2012): some studies (Geda et al., 2002; Nikolaos et al., 2004; Chuang et al., 2012) found no effect on plasma concentrations of total cholesterol, high-density lipoprotein cholesterol, or its components, whereas others demonstrated significant changes in lipids, lipoproteins, and apolipoproteins (Demircioglu et al., 2000; Voudris et al., 2006; Abaci et al., 2009; Grosso et al., 2009; Verrotti et al., 2010); in particular, Abaci et al. found a significant increase in total cholesterol and LDLs after 12 months of VPA treatment, but triglycerides and HDLs levels did not change. High serum triglyceride concentrations and low HDL were found in patients on VPA treatment which have developed the MS, and there were no significant differences by gender (Verrotti et al., 2010). In this work, the dyslipidemia was associated with the IR; in fact, it is known that hyperinsulinemia increases lipogenesis that can be responsible for the accumulation of triglycerides: insulin plays a central role in determining triglyceride clearance from the blood via activation of lipoprotein lipase and triglyceride output through effects on the synthesis and secretion of very LDL (VLDL) by the liver (Lewis and Steiner, 1996). Furthermore, insulin controls the output of free fatty acids from adipose tissue (Arner, 1995); consequently, a state of IR may determine a delay in plasma lipoprotein triglyceride clearance, that allows for cholesterol esters to be passed on from HDL to triglyceride-rich particles, which results in potentially atherogenic lipoprotein particles (Patsch et al., 1992).

Homocysteine (Hcy) is a sulfur-containing, nonprotein amino acid reversibly formed and secreted during metabolism of methionine. Once formed, Hcy is metabolized via two pathways: (i) re-methylation to methionine, which requires methylenetetrahydrofolate reductase (MTHFR)/methionine synthase (MS) or betaine homocysteine methyltransferase (BHMT), and folic acid and vitamin B12 as co-factors; (ii) trans-sulfuration to cysteine, which requires cystathionine-beta-synthase (CBS) and pyridoxal-5'-phosphate, the vitamin B6 coenzyme (Mattson and Shea, 2003; Belcastro et al., 2007; Belcastro et al., 2010). Epidemiological data demonstrated that elevated hyper-Hcy concentration is an independent risk factor for the progression of atherosclerosis (Temple et al., 2000; Hassan et al., 2004; Belcastro and Striano, 2012). In particular, hyper-Hcy has been associated with cardiovascular disease and stroke in multiple large-scale epidemiologic studies (Belcastro and Striano, 2012). Notably, it has been showed that, among older AEDs, prolonged treatment with VPA raises tHcy levels in epileptic children (Verrotti et al., 2000; Karabiber et al., 2003; Attilakos et al., 2006).

Finally, it has been shown that uric acid level was significantly higher in patients with VPA monotherapy; it is known that higher levels of serum uric acid may be associated with the development of atherosclerosis that is independent of other atherosclerotic risk factors.

Conclusions

Since its first marketing as an antiepileptic drug more than 45 years ago in France, VPA has become established worldwide as one of the most widely used AEDs in the treatment of both generalized and partial seizures in adults and children. The broad spectrum of antiepileptic efficacy of VPA is reflected in preclinical in vivo and in vitro models, including a variety of animal models of seizures or epilepsy. VPA may have many adverse effects (usually considered idiosyncratic) that require vigilance during the chronic treatment: in particular, its use is not recommended in patients with some preexisting conditions e.g. hepatic and pancreatic insufficiency; moreover, VPA is clearly associated with weight changes and related endocrine abnormalities: therefore, this drug should be avoided in obese patients (at risk of developing MS), in particular in female pubertal patients because VPA can be expected to cause polycystic ovaries. Moreover, increase weight may account for increase of atherosclerosis risks: consequently, this drug should be avoided in a familiar context of atherosclerosis and/or cardiovascular diseases.

There is no single mechanism of action of this AED that can account for all the numerous effects of the drug on neuronal tissue and its broad clinical activity. Furthermore, by the experimental and clinical observations summarized in this review, the potential many endocrinological and metabolic side effects of VPA remain to be explained. Changes involving the levels of key molecules or neurotransmitters such as insulin, leptin, neuropeptide, ghrelin, and adiponectin may influence weight gain and VPA-induced obesity with the subsequent metabolic consequences. In view of the advances in molecular neurobiology and neuroscience, future studies will hopefully further our understanding of the mechanisms of action of this amazing drug.

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