Mini Review

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Valproate-Induced Insulin Resistance and Obesity in Children

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Key Words
Epilepsy · Valproate · Obesity · Insulin resistance · Leptin

Abstract
Background: Valproic acid (VPA), a widely used antiepileptic drug, has broad-spectrum activity against both generalized and partial epilepsy. Among the side effects of VPA, weight gain is frequently reported, although the real incidence and magnitude of this problem is unknown. Its pathogenesis is most likely multifactorial, and is controversial. ***Methods:*** In order to evaluate the role of hyperinsulinemia and related hormonal abnormalities in VPA-induced obesity, data from the existing literature have been analyzed and discussed critically. ***Results:*** Patients suffering from weight gain show various metabolic and endocrinologic abnormalities. The most frequent are hyperinsulinemia and insulin resistance, hyperleptinemia and leptin resistance, and an increase in the availability of long-chain free fatty acids. Significant weight gain is associated with increased levels of insulin and leptin, suggesting a close relationship between obesity-induced hyperinsulinemia and hyperleptinemia. VPA can directly stimulate pancreatic β-cells and indirectly enhance insulin resistance by suppressing insulin-mediated peripheral glucose uptake. Leptin activation seems to be similar in obese VPA-treated subjects to that seen in otherwise obese subjects. ***Conclusions:*** The mechanisms of hyperinsulinemia in VPA-induced weight gain remain unclear, although it is likely that obesity is the cause of hyperinsulinemia and all related metabolic changes. However, this heterogeneous metabolic disorder requires further research.

Introduction

Epilepsy is one of the most common neurological diseases. Valproate (VPA) is a widely used broad-spectrum antiepileptic drug, and it is increasingly used for other indications, such as bipolar psychiatric disorder and migraine prophylaxis [1, 2]. VPA treatment is often long term, highlighting the importance of evaluating its safety. One of the most common side effects is weight gain, which is frequently associated with important metabolic and endocrine abnormalities.

The aim of this review is to discuss the main mechanisms of VPA-induced obesity and to analyze the possible endocrinological consequences.

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Table 1. Obesity, serum insulin and insulin resistance in VPA-treated patients in recent published studies

Author	Patients	Age, years	Daily dosage	Duration of therapy years	Patients who gained weight, %	Fasting serum insulin	Insulin resistance
Egger (1981)	100 (M/F)	1.25 – 18.0[a]	30 – 50 mg/kg[a]	0.5 – 5[a]	44.0	NR	NR
Verrotti (1999)	40 (F)	17.3 ± 1.2	30 – 50 mg/kg[a]	1	37.5	↑	+
Novak (1999)	25 (M)	1.8 – 16.9[a]	375 – 2,500 mg[a]	0.72 – 2.82[a]	10.91	NR	NR
	30 (F)		250 – 2,000 mg[a]				
Rattya(1999)	40 (F)	8.4 – 18.5[a]	8.7 – 27.5 mg/kg[a]	0.8 – 8[a]	50.0	↑	+
Demir (2000)	20 (M/F)	3.5 – 15.0[a]	10 – 20 mg/kg[a]	0.25[a]	55.0	↑	+
Stephen (2001)	23 (F)	33[b] (F)	400 – 2,500 mg[a]	≥2	29.2	↑	NR
	17 (M)	29[b] (M)	800 – 4,500 mg[a]		16.4		
Biton (2001)	68 (M/F)	30.1 ± 14	633 ± 1.82 mg	0.67[b]	62.22	NR	NR
Verrotti (2002)	20 (F)	8.5 – 11.2[a]	30 mg/kg	1	35.1	↑	+
Pylvanen (2002)	81 (M/F)	29.6 ± 10.9	1,126 ± 311 mm	6.5 ± 4.9	49.0	↑	NR
Luef (2002)	22 (F)	31.2 ± 4.2	975 mg[b]	13.5 ± 6.5	45.45	↑	NR
Elaine (2003)	46 (M/F)	10 – 17[a]	18 mg/kg[b]	1.42[b]	58.14	NR	NR
Pylvanen (2003)	37 (M)	28.7 ± 2.1	413 ± 1.219 mg	0.5 – 15[a]	54.05	↑	NR
Biton (2003)	20 (M/F)	16.0 ± 3.0	100 – 500 mg[a]	0.67[b]	70.0	NR	NR
Mikkonen (2005)	40 (F)	12.5 ± 3.1		5.8[b]	21.0	NR	NR
Pylvanen (2006)	31 (M)	30.4 ± 11.4	1,098.3 ± 352.5 mg	5.8 ± 3.9	52.94	↑	+
	20 (F)	32.8 ± 12.8	997.4 ± 358.9 mg	7.4 ± 6.2			
De Vries (2007)	43 (F)	14.9 ± 3.3	12.20 ± 4.54 mg/kg	1 – 9.5[a]	25.58	Normal	–
El-Khatib (2007)	51 (M)	35.0 ± 13.1	1,255 ± 526 mg	1.8 ± 0.5	27.5	Normal	–
	55 (F)	34.0 ± 10.0	1,141 ± 498 mg	1.5 ± 0.7	56.4		
Prabhakar (2007)	25 (F)	18.3 ± 3.7	724 ± 150.8 mg	1	72.0	NR	NR
	11 (F)			2	54.55		
	6 (F)			2.75 – 3[a]	50.0		

NR = Not reported; + = present; – = absent. [a] Range values; [b] median values; [c] mean values.

Valproate and Weight Gain

Epidemiology

Marked weight gain can occur during treatment with VPA and should be of concern to the clinician because it can lead to many endocrinological problems.

Egger and Brett [3] noted weight gain in 44 of the 100 children treated with VPA. Increased appetite and excessive weight gain were reported in 23 boys and 21 girls; 31 of 66 patients with generalized epilepsy and 13 of 34 with partial epilepsy were affected in this way. In the following years, many studies [3–20] quantified the amount of weight gain. Also, in our experience we have found that the percentage of obesity in a group of 40 epileptic patients without mental retardation is significantly higher in VPA-treated patients (37.5%) than in a group of 40 epileptics treated with other anticonvulsant drugs (10%). The main studies and the percentage of weight gain observed are presented in table 1.

Related Factors

Duration of VPA Treatment

Weight gain due to VPA treatment is usually observed during the first 3 months of therapy [8, 12], reaching a maximum after 6 months [3, 21–23]. In contrast, data from many studies [3, 12, 16, 17, 20] make it clear that patients with weight gain received the medication for a significantly longer time than those who did not gain weight. In conclusion, a long duration of therapy is associated with significant weight gain that continues after the first rapid increase in the first months of therapy.

Gender

Women seem to be more prone to weight gain during VPA therapy than men. It is possible that this gender difference could be related to leptin resistance or to the high frequency of carbohydrate craving observed in VPA-treated patients [19]. This higher percentage of weight

gain in female patients is clearly reported by many authors [3, 5, 7, 9, 17, 19, 21]. In particular, a possible effect of gender on the extent of weight gain has been studied by El-Khatib et al. [19], who compared the incidence and extent of weight gain associated with VPA monotherapy in male and female epileptic patients. This study demonstrated a more pronounced and more frequent weight gain in women receiving VPA monotherapy, compared with men. The authors reported a significant weight gain (≥5 kg) in 43.6% of women compared with 23.5% of men on VPA therapy.

Daily Dosage

Although not all studies have analyzed the role of VPA dosage, the literature [5–7, 17, 24], as well as our experience [4], demonstrate that there is no correlation between the degree of weight gain and the daily VPA dosage and/or serum VPA concentration.

Puberty

The increase in body weight appears to occur most frequently in post-pubertal girls taking VPA [3, 4, 6, 8, 9, 12, 15, 17, 19, 20, 25–27], although VPA-induced weight gain has also been reported also in pre-pubertal patients [4–7, 10, 24, 26, 28]. Finally, a recent population-based study reported that increase in body weight is more common in patients treated with VPA during puberty if epilepsy and medication continue into adulthood [16].

Seizure Type and Neurocognitive Status

Apart from one study that showed that patients with generalized versus partial seizures tend to be at greater risk for weight increase [13], the literature does not differentiate the incidence of weight gain between generalized and partial epilepsy patients [8, 9, 11, 14, 17, 19, 28, 29]. Our experience confirms this lack of a difference [4]. Moreover, abnormal neurocognitive status does not appear to represent a risk factor for obesity [19, 22].

Anthropometric Measures

A predictor of an overweight BMI category at follow-up is a potentially overweight BMI category at onset. In fact, some studies showed that the greater the patient's initial weight, the more it will increase during treatment with VPA [5, 13, 16].

Possible Mechanisms Underlying VPA-Induced Weight Gain

In spite of the studies mentioned above, unsolved problems remain. In fact, the real pathogenetic mechanism underlying VPA-induced weight increase is still unclear. Several mechanisms have been suggested to explain VPA-related weight gain, including:

(1) The effect of VPA on the hypothalamus. This hypothesis is supported by the observation that VPA-treated epileptic patients who reported weight gain developed increased appetite, thirst, and quenching with calorie-rich beverages [7, 22, 30, 31]. All these behaviors can indicate hypothalamic stimulation [32]. Moreover, experimental data demonstrate that VPA can cause dysregulation of the hypothalamic system [33–35]: in particular, an in vitro study showed that VPA may exert part of its therapeutic effect as a mood-stabilizing drug by modulating the hypothalamic secretion of corticotrophin-releasing factor [34]. More recently, a study carried out in the Wistar strain female rats shows that treatment with VPA disrupts the hypothalamo-hypophyseal-gonadal axis at the level of the GnRH pulse generator in the hypothalamus [33]. Although this theory can explain weight gain related to some GABA-enhancing drugs including VPA and gabapentine [15], this is not the sole mechanism. Other antiepileptic drugs that increase GABA, such as tiagabine, do not induce weight gain [36].

(2) VPA-induced hyperleptinemia and leptin resistance. Leptin is a signal factor that regulates body weight through neuropeptide Y, which stimulates food intake and decreases thermogenesis [37–40]. A strong correlation has been observed between serum leptin concentration, BMI, and body fat mass in humans [41]. Leptin resistance is defined as reduced sensitivity or complete insensitivity to leptin action that probably contributes to altering leptin signaling and decreases negative feedback [42, 43]. Conversely, human subjects with insulin resistance have high concentrations of serum leptin [44]. It has been suggested that VPA-related obesity may be associated with elevated serum insulin and leptin levels in women with epilepsy [4, 21]. We demonstrated that after 1 year of VPA treatment, obese patients had significantly higher serum leptin and insulin levels compared with patients who did not gain weight. We found no significant correlation between serum VPA concentration and leptin levels, or between serum VPA and insulin concentration. In contrast, a significant correlation was present between BMI and leptin, and between leptin and fasting insulin [4]. In our study, only obese VPA-treated patients had

higher levels of leptin with respect to their pre-treatment evaluation. Non-obese VPA-treated patients continued to show normal leptin levels. Therefore, VPA therapy itself does not appear to cause the alteration of leptin levels in those patients who remain non-obese. Thus, despite a recognition in the literature of the association of hyperinsulinemia and VPA-induced obesity, it is unclear whether leptin behavior in VPA-induced obesity is similar to that in any other obesity situation. Some data support this hypothesis. First, as previously reported in healthy obese patients [45–49], the mean serum leptin concentration increases with weight gain [4, 5, 10, 11, 18, 29]. Second, in a study carried out by Pylvanen et al. [11], serum leptin levels did not differ between obese patients taking VPA and obese control subjects, suggesting that leptin activation is similar in the two groups. Third, analyses of patients who gained weight during VPA therapy revealed significantly higher serum leptin concentrations in women compared with men [11, 19]. This is in accordance with reports indicating that healthy obese women have higher leptin levels compared with men [41].

In contrast, some studies have failed to demonstrate a significant correlation between BMI and the leptin levels in epileptic patients [4, 14, 19] while such a correlation is generally present in healthy obese subjects [41]. Moreover, Lagace et al. [50] tested the effects of VPA on leptin biology and fatty acid metabolism in 3T3-L1 adipocytes and reported that VPA significantly reduced leptin secretion in a dose-dependent manner. In particular, the authors noted that VPA appears to decrease the levels of leptin mRNA in adipocytes without affecting mRNA degradation.

In conclusion, VPA can modify leptin levels through the increase of body weight, and this modification is related to BMI. In the absence of VPA-induced obesity, no significant changes in leptin levels have been observed.

(3) VPA and adiponectin. Adiponectin is an adipocyte-derived protein that plays an important role in controlling insulin sensitivity and glucose homeostasis. It is the most abundant adipose tissue protein expressed from the adiponectin gene transcript-1. Some experimental data suggest a possible interaction between VPA and adiponectin [51].

Recently, we demonstrated that adiponectin levels were significantly lower in obese epileptic patients compared with those who did not gain weight, suggesting that patients who showed VPA-induced obesity had similar changes in adiponectin and ghrelin observed in essential obesity [52].

Qiao et al. [53] examined the effects of VPA on adiponectin gene expression in C57BL/6J mice and in differentiated 3T3-L1 adipocytes. They found that VPA inhibited adiponectin gene expression in mature adipocytes. This inhibitory effect was dose- and time-dependent, and occurred through the inhibition of histone deacetylase activity, one of the several enzymatic activities involved in the transcriptional regulation of DNA.

(4) VPA-induced hyperinsulinemia and insulin resistance (see below).

(5) Genetic factors may influence changes in body weight during VPA therapy. This hypothesis is supported by the observation of five pairs of monozygotic twins treated with VPA therapy. With the exception of one pair, the weight course within each pair of twins was similar during therapy with VPA. Two pairs gained weight to a comparable extent. The other pair reached the same final weight, although VPA was started at different initial weights. The increase was higher in the twin with the lower starting weight [54]. Similarly, it has been reported [55] that weight gain under VPA is higher in patients with lower starting weight although the majority of the studies [5, 13, 15, 16, 23] have demonstrated simply that the risk of obesity is magnified in those patients who have a higher weight at the start of treatment.

VPA and Insulin Resistance

Definition of Insulin Resistance and Methods of Assessments

Insulin resistance is generally defined as a state of inefficient insulin function in skeletal muscle, liver, and adipocytes, with reduced responsiveness of these organs to normal circulating insulin levels. Therefore, this condition is typically associated with elevated fasting and post-prandial insulin levels [11].

The standard technique for assessing insulin sensitivity is the hyperinsulinemic euglucemic clump [56–58]. Although clump technology has been applied to the study of insulin sensitivity and insulin secretion during childhood, it is an invasive tool. Therefore, several fasting or 'homeostatic' models have been proposed: the homeostatic model assessment (HOMA), the fasting glucose/insulin ratio (FGIR), and the quantitative insulin sensitivity check index (QUIKI) methods [57–59]. It is very difficult to compare the data from the various studies in epileptic patients. While a large majority of authors report fasting serum insulin concentrations in VPA-treated

patients, insulin resistance has been assessed by different methods.

Link between VPA and Insulin Resistance

In 1996, Isojärvi et al. [21] found that VPA-treated women who developed obesity were hyperinsulinemic. Similarly, in women receiving VPA treatment for bipolar disorder, insulin and leptin levels are significantly elevated when compared with women on lithium therapy [45, 60]. The same authors, a few years later (2002), studied insulin sensitivity in prepubertal girls who gained weight after 1 year of VPA therapy. At the end of the study the obese patients had significantly higher serum insulin levels compared with patients who did not gain weight.

In adult patients, Luef et al. [12] confirmed in 2002 that the VPA group showed a significantly higher BMI and post-prandial insulin levels compared with the control group. Moreover, the same difference was observed after OGTT. These results led the authors to suspect that therapy with VPA, through a GABAergic agonist mechanism, is associated with increased stimulated secretion of glucose, which may be followed by an increase in body weight.

Furthermore, when compared with patients treated with other antiepileptic drugs, VPA-treated patients show higher post-prandial insulin and C-peptide levels [29].

In the same period, Pylvanen et al. [11] showed that both obese and lean patients taking VPA had hyperinsulinemia, suggesting a development of insulin resistance as the leading factor to weight gain during VPA treatment. It is difficult to explain the presence of hyperinsulinemia in lean patients. For this reason, more recently, the same authors [61] strengthened these results by studying 51 adult patients on VPA monotherapy and comparing them with 45 healthy control subjects with respect to fasting plasma glucose, serum insulin, proinsulin, and C-peptide concentrations after overnight fast. The VPA patients had fasting hyperinsulinemia, although the fasting serum proinsulin and C-peptide concentrations were not significantly higher compared with the control subjects. Therefore, the authors suggested that VPA does not induce insulin secretion but may interfere with insulin metabolism in the liver, resulting in higher insulin concentrations in peripheral circulation. These changes were also seen irrespective of concomitant weight gain, suggesting that increased insulin concentrations induce weight gain whereas the reverse is not true.

In the hypothesis of VPA-induced insulin resistance, these authors [61] also studied the lipid profile of the same patients and the possibility of a metabolic syndrome related to VPA therapy. They found that VPA-treated patients also had higher concentrations of triglycerides and uric acid, and lower levels of high-density lipoprotein cholesterol compared with control subjects.

Etiopathogenetic Hypotheses of VPA-Induced Insulin Resistance

All these results confirm the VPA side effect on insulin metabolism with consequent insulin resistance. However, the exact pathogenesis is still not fully clarified. Several mechanisms have been proposed.

VPA and Fatty Acids

VPA is a branched chain fatty acid and, therefore, it can compete with FFAs for albumin binding, increasing their local availability and thus their physiological modulation of insulin secretion. Elevated FFAs impair insulin biosynthesis and increase the proinsulin/insulin ratio of secretion [29]. A condition of increased FFAs levels, such as occurs with VPA therapy, plays an important role in the development of insulin resistance. It is well known that both dietary intake and plasma levels determine the fatty acid composition of cell membranes, and higher levels of membrane saturated fatty acids seem to impair the action of insulin, whereas the presence of polyunsaturated fatty acids (especially the ω–3 and the ω–6 families) improves insulin sensitivity [62].

If this is correct, any perturbation that results in the accumulation of fatty acid derivatives within muscle and liver, such as therapy with the unsaturated fatty VPA, could induce insulin resistance.

VPA and Insulin Signal Transduction Pathway

Wong et al. [63] tested the hypothesis that VPA can inhibit GLUT-1, one of the five proteic glucose carriers on the cell membrane activated at the end of the insulin transduction signal. Their study showed that VPA inhibited GLUT-1 activity in normal astrocytes and fibroblasts, with an important reduction of glucose transport accompanied by an up to 60% downregulation of GLUT-1 mRNA expression. Finally, it has been demonstrated that VPA can directly stimulate the pancreatic β-cells. In fact, Luef et al. [64] investigated the effect of VPA on insulin secretion in pancreatic islet cells from pancreases of multiorgan donors: the incubation with VPA caused a time- and dose-dependent increase of insulin concentration in cell supernatant, suggesting that VPA can directly induce hyperinsulinemia.

Conclusions

Weight gain is a possible side effect of VPA; although this problem has been not observed in all patients, sometime it can limit its use in clinical practice and possibly causing various metabolic disturbances. The mechanism of VPA-induced weight gain remains to be determined, but the association between VPA therapy and hyperinsulinemia has received great interest. Weight gain during VPA treatment is related to an increase in insulin levels. This hyperinsulinemia and the consequent insulin resistance are strictly related to the degree of obesity.

Insulin resistance is frequently associated with the presence of high serum leptin levels, and leptin-induced weight gain probably occurs through an insulin resistance effect. It is likely that the endocrine changes observed in epileptic patients treated with VPA are secondary to excess fat mass because, generally, these changes are found only in those epileptic patients who gained weight. Moreover, it has been demonstrated that VPA can directly stimulate pancreatic β-cells. In fact, in recent years, VPA was recognized as a potent drug able to interact with gene expression of many proteins, including insulin, leptin and adiponectin. Well-designed animal and human studies are needed to better understand the relationship between weight gain and metabolic disturbances, and to enhance our knowledge about this drug.

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