Increase in Postprandial Serum Insulin Levels in Epileptic Patients With Valproic Acid Therapy

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A significant weight gain and increase in serum leptin levels in the course of antiepileptic treatment with valproic acid (VPA) has been described in several clinical studies. With respect to the long treatment period in antiepileptic therapy, these side effects might increase insulin resistance and metabolic risk factors. We have studied clinical and laboratory effects of VPA treatment in a cohort of female patients (n = 22) and in patients treated with carbamazepine (CBZ) or lamotrigine monotherapy (n = 21). All study participants underwent an oral glucose tolerance test (OGTT) with 75 g glucose. Body mass index (BMI) in the VPA group was higher (28.1 ± 3.6 kg/m^2) than in the control group (23.9 ± 3.7 kg/m^2) ($P < .039$). While plasma glucose, serum leptin, insulin, and C-peptide levels did not differ significantly between the study groups in the fasting state, postprandial (pp) insulin and proinsulin levels were found to be significantly higher in the VPA than in the control group. In the course of the OGTT, serum insulin levels reached their peak values 1 hour postprandially with 68.8 ± 10.0 μU/mL in the VPA group and 49.8 ± 11.2 μU/mL in the control group ($P < .042$). After 2 hours, the corresponding serum insulin levels were 48.5 ± 25.2 μU/mL and 34.1 ± 17.2 μU/mL ($P < .048$) and the proinsulin levels 52.5 ± 30.2 pmol/L and 29.5 ± 12.0 pmol/L ($P < .017$). While BMI values in the non-VPA group showed a significant correlation only with the fasting values of insulin, proinsulin, and C-peptide, the BMI values of the VPA-treated group were also positively related to the 2-hour pp levels of insulin ($R = .690$; $P < .001$), proinsulin ($R = .667$; $P < .001$) and C-peptide ($R = .502$; $P < .017$). VPA is a fatty acid derivative, competes with free fatty acids (FFA) for albumin binding, and acts as a gamma aminobutyric acid (GABA)-ergic agonist, mechanisms, which are known to be involved in pancreatic β-cell regulation and insulin secretion. Therefore, it might be suspected that VPA therapy is associated with increased glucose stimulated pancreatic secretion and thus a higher body weight in the VPA group.

ANTIEPILEPTIC DRUG THERAPY with valproic acid (VPA), an effective anticonvulsant, was found to be associated with an increase in body weight, paralleled by increased serum insulin and leptin levels.[1-3] The weight gain and the associated increase in insulin resistance might result in an increase in patients' cardiovascular risk.[4,5] Various adipose tissue products have recently been defined as a link between increased body weight and the development of insulin resistance. Leptin, the gene product of the obese gene, signals the size of adipose tissue mass, inhibits appetite, and promotes metabolism.[6] Serum leptin levels show a positive correlation with serum fasting insulin and with blood pressure values.[7-9] Other than the close relationship of leptin to obesity-induced insulin resistance,[10] a modulation of pancreatic insulin secretion by leptin could also be demonstrated.[11,12] Obese human subjects show high serum leptin levels and thus obesity seems to be associated with at least a partially decreased sensitivity to leptin.[8,13] Also, other adipose tissue products, especially the cytokine tumor necrosis factor (TNF)-α[14,15] and interleukin,[16] were found to reduce insulin sensitivity. In an insulin-resistant state, increased lipolysis and reduced re-esterification of free fatty acids (FFA) in adipose tissue results in increased serum levels of FFA.[17,18] Prolonged elevation of FFA further enhances insulin resistance by suppressing insulin-mediated peripheral glucose uptake[19] and also affects pancreatic insulin secretion.[20,21]

With respect to the weight gain induced by VPA therapy and the fact that VPA is a fatty acid derivative[22-24] competing with FFA for albumin binding,[25] it seemed to us of interest to study the relationship of VPA therapy to symptoms of insulin resistance[1,4,5] and to plasma insulin levels in the course of an oral glucose tolerance test (OGTT).

SUBJECTS AND METHODS

Study Subjects

We have studied 43 age-matched women with epilepsy. They had different types of epilepsy syndromes and were followed at the Department of Neurology, University of Innsbruck, Innsbruck, Austria. Twenty-two patients were on monotherapy with VPA, the remaining 21 were treated with other antiepileptic drugs, including carbamazepine (CBZ) (15 patients) and lamotrigine (6 patients). Patients started antiepileptic drug therapy after 2 unprovoked seizures. Body mass index (BMI), waist-to-hip ratio (WHR), and blood pressure values were determined in all patients at the clinical visits. None of the patients included in our study was on oral contraceptives. Clinical data and laboratory results were obtained during the follicular phase of the menstrual cycle.

With respect to the routinely performed laboratory data, all patients participating in the study showed normal blood counts, as well as normal electrolyte levels, liver, and kidney function tests. None of the study participants suffered from diabetes or concurrent disease, such as acute infections, thyroid dysfunction, autoimmune or chronic inflammatory diseases, tumors, or hepatic disorders. None of the patients was pregnant.

All of the 21 women treated with VPA had the diagnosis of idiopathic generalized epilepsy, while 13 of the 15 patients treated with CBZ had temporal lobe epilepsy and the remaining 2 symptomatic

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Table 1. Patients Characteristics

	Patients Treated With VPA (n = 22)	Patients Treated With Other Antiepileptics (n = 21)	*P* Value
Age (yr)	31.2 ± 4.2	32.2 ± 5.6	NS
BMI (kg/m^2)	28.1 ± 3.6	23.9 ± 3.7	.039
Waist-to-hip ratio	0.80	0.80	NS
Blood pressure (mm Hg)	Systolic: 111.0 ± 8.1	Systolic: 111.0 ± 10.8	NS
	Diastolic: 74.0 ± 5.7	Diastolic: 72.0 ± 6.7	NS
Total cholesterol (mg/dL)	187.8 ± 31.7	214.2 ± 35.8	.010
Triglycerides (mg/dL)	110.2 ± 76.2	101.1 ± 37.4	NS
LDL-cholesterol (mg/dL)	100.3 ± 32.0	118.0 ± 40.0	NS
HDL-cholesterol (mg/dL)	67.0 ± 18.6	76.0 ± 26.3	NS

Abbreviation: NS, not significant.

epilepsy of other origin. Four of the 6 lamotrigine patients suffered from idiopathic generalized epilepsy, and the remaining 2 had focal epilepsies.

The antiepileptic drugs were prescribed at an average dosage, and all patients showed plasma drug levels within a stable therapeutic range. Duration of treatment lasted from 3 to 27 years (mean, 12 years).

According to the recommendations of the local Ethical Committee, informed consent was obtained from the patients after the purpose of the study was described to them.

Laboratory Procedures

Laboratory controls were performed in the morning after a 10-hour overnight fasting period. Serum samples from all study participants were stored at –70°C. Plasma glucose, liver, and kidney function tests were measured according to routine procedures.

The OGTT was performed by a glucose load with 75 g glucose, plasma glucose, serum insulin, proinsulin, C-peptide, and leptin levels were determined in the fasting state and 2 hours postprandially. Plasma glucose was measured enzymatically, as well as serum cholesterol and triglyceride levels (Cholesterol PAP, MA Kit; Roche; triglycerides PAP, UNI-Kit II; Roche, Vienna, Austria). High-density lipoprotein-cholesterol (HDL-C) was determined using a precipitation procedure with dextrane sulfate and magnesium chloride,[26] and low-density lipoprotein-cholesterol (LDL-C) was calculated according to the Friedewald formula.[27] Serum samples for leptin were measured in duplicate with a double-antibody radioimmunoassay (RIA; Human Leptin RIA Kit; Linco Research, St Charles, MO). Serum insulin was determined by the IMx insulin assay (Abbott, Vienna, Austria), which is based on the microparticle enzyme immunoassay technology and shows no cross-reactivity with proinsulin. C-peptide levels were measured by a RIA (C-PEP-RIA-CT; Biosource, Fleurus, Belgium), and Proinsulin by enzyme-linked immunosorbent assay (ELISA) technology (Proinsulin ELISA, Mercodia, Uppsala, Sweden).

As a measurement for insulin resistance, homeostasis model assessment (HOMA) was determined by fasting plasma glucose (mmol/L) × fasting serum insulin (μU/mL)/22.5.[28,29]

Serum antiepileptic drug levels of VPA and CBZ were measured by fluoresencepolarization (TDX analyzer, Abbott) technology.

Statistics

Data are presented as mean ± SD. Differences between the groups were tested using the Mann-Whitney *U* test, and the .05 levels of probability were taken to be statistical significant. Relationships between variables were evaluated by the Pearson correlation coefficient. All analyses were performed with the SPSS for Windows statistical package (SPSS, Chicago, IL).

RESULTS

BMI was higher in the VPA-treated group (28.1 ± 3.6 kg/m^2) than in patients on therapy with other antiepileptic drugs (23.9 ± 3.7 kg/m^2) ($P < .039$) (Table 1). Fasting and postprandial (pp) serum leptin levels were also higher in the VPA group (17.3 ± 15.8 ng/mL and 16.2 ± 15.8 ng/mL; respectively) than in the control group (10.8 ± 8.0 ng/mL and 9.3 ± 7.4 ng/mL; respectively), but these differences did not reach statistical significance ($P < .091$ and $P < .075$) (Table 2).

Plasma glucose levels in the fasting and pp state showed no significant differences between the study groups (Tables 2 and 3). Fasting serum insulin and C-peptide levels did not differ between VPA-treated patients and those on other antiepileptic

Table 2. Metabolic Parameters in Patients Treated With VPA and Other Antiepileptic Substances

	Patients Treated With VPA	Patients Treated With Other Antiepileptis	*P* Value
Fasting glucose (mg/dL)	80.8 ± 10.1	83.3 ± 8.7	NS
2-hour pp glucose (mg/dL)	96.2 ± 19.9	83.7 ± 21.3	NS
Fasting serum C-peptide (pmol/mL)	0.7 ± 0.2	0.6 ± 0.2	NS
2-hour pp serum C-peptide (pmol/mL)	2.9 ± 1.0	2.3 ± 0.9	.050
Fasting serum proinsulin (pmol/L)	7.1 ± 3.53	5.3 ± 1.8	.065
2-hour pp serum proinsulin (pmol/l)	52.5 ± 30.2	29.5 ± 12.0	.017
Fasting serum leptin levels (ng/mL)	17.3 ± 15.8	10.8 ± 8.0	NS
2-hour pp serum leptin levels (ng/mL)	16.2 ± 15.8	9.3 ± 7.4	.091
HOMA index	1.5 ± 0.7	1.3 ± 0.8	.119

Table 3. OGTT in Patients Treated With VPA and Other Antiepileptic Substances

	Patients Treated With VPA	Patients Treated With Other Antiepileptics	*P* Value
Glucose (mg/dL)			
Fasting	80.8 ± 10.0	83.3 ± 8.7	NS
30-min pp	146.3 ± 8.7	149.8 ± 11.0	NS
60-min pp	122.4 ± 7.8	129.0 ± 9.4	NS
90-min pp	117.8 ± 12.2	124.6 ± 10.4	NS
120-min pp	96.2 ± 19.9	83.7 ± 21.3	NS
Serum insulin (μU/mL)			
Fasting	6.9 ± 2.5	6.5 ± 3.1	NS
30-min pp	64.6 ± 8.4	32.0 ± 12.2	<.021
60-min pp	68.8 ± 10.0	49.8 ± 11.2	<.042
90-min pp	61.3 ± 9.5	39.7 ± 7.8	<.030
120-min pp	48.5 ± 25.2	34.1 ± 17.2	<.048

drugs, while the pp insulin levels obtained in the course of an oGTT, as well as the 2-hour C-peptide levels, were significantly higher in the VPA group than in the control group (Tables 2 and 3). Fasting and especially 2-hour pp proinsulin levels were significantly higher in VPA-treated patients (52.5 ± 30.2 pmol/L) than in patients on other antiepileptic drugs (29.5 ± 12.0 pmol/L; $P < .017$).

BMI in the VPA, as well as in the non-VPA group, showed a strong positive correlation to fasting and 2-hour pp serum leptin levels (Table 4). While in the non-VPA group, BMI values were positively related to insulin, proinsulin, and C-peptide values only in the fasting state. BMI of the VPA-treated patients showed a significant positive correlation also with the 2-hour pp insulin ($R = .690$; $P < .0019$), proinsulin ($R = .667$; $P < .001$) and C-peptide levels ($R = .502$; $P < .017$) (Table 4) . Only in VPA-treated patients, a significant positive correlation between BMI values and fasting ($R = .433$; $P < .044$), as well as pp ($R = .609$; $P < .003$) glucose values was demonstrted (Table 4).

Total cholesterol and LDL-C levels were higher in the non–VPA-treated patients (Table 1), while the VPA group showed higher triglyceride and lower HDL-C values, but these differences did not reach statistical significance. Blood pressure values were normal in both groups (Table 1). WHR did not differ between VPA therapy and the control group.

The HOMA index as a parameter of insulin resistance was 1.5 ± 0.7 in the VPA-treated group and 1.3 ± 0.8 in the group treated by CBZ or lamotrigine ($P < .119$).

DISCUSSION

Our results of an increased BMI in VPA-treated patients are in accordance with several previously published studies.[1-4] The precise mechanism underlying the VPA-associated weight gain, however, remains unclear. Leptin, a hormone secreted by adipose tissue, acts primarily to inhibit appetite and promotes metabolism,[6] while overfeeding results in increased serum leptin concentrations indicating leptin resistance.[7,8] Leptin, as well as the cytokine TNF-α, are both products of the adipose tissue and increase insulin resistance by interfering with the insulin receptor postreceptor pathway.[5,10,30] Insulin resistance is paralleled by an increase in plasma levels of FFA.[17,19] As signaling molecules to the nuclear peroxisome-activated receptors, FFA lead to an increased expression of leptin and TNF-α mRNA in adipose tissue.[17,31] While VPA treatment is associated with an increase in serum leptin levels,[2] the production of TNF-α and interleukin was found to be reduced.[32] In our evaluation, no significant differences in serum leptin levels could be observed between patients treated with VPA and the control group, and the BMI showed a significant positive correlation to serum leptin values in both treatment groups. Thus, additional mechanisms seem to be involved in the weight gain during VPA therapy.

Valproate is a fatty acid derivative,[22-24] and fatty acids also modulate pancreatic insulin secretion.[20,21,33] Because VPA was shown to compete with FFA for albumin binding,[25] it could be hypothesized that either an increased local availability of FFA under VPA therapy or VPA itself alter pancreatic insulin secretion. Elevated FFA also impair insulin biosynthesis and increase the proinsulin/insulin ratio of secretion.[20,33] In our VPA-treated group, pp proinsulin levels increased more than the corresponding pp insulin levels. Plasma glucose, fasting insulin, and C-peptide levels, as well as the resulting HOMA index as a measure for insulin resistance, did not differ between the VPA-treated patients and the control group, while pp insu-

Table 4. Correlation of BMI to Leptin, Glucose, and Insulin Serum Levels

		BMI in VPA-Treated Patients	BMI in Patients Treated With Other Antiepileptics
		Correlation (*P* value)	Correlation (*P* value)
Leptin	Fasting	$R = .630$ (.002)	$R = .894$ (.001)
	2-hour pp	$R = .615$ (.003)	$R = .908$ (.001)
Glucose	Fasting	$R = .433$ (.044)	$R = .268$ (NS)
	2-hour pp	$R = .609$ (.003)	$R = .225$ (NS)
Insulin	Fasting	$R = .573$ (.005)	$R = .686$ (.001)
	2-hour pp	$R = .690$ (.001)	$R = .063$ (NS)
Proinsulin	Fasting	$R = .652$ (.001)	$R = .627$ (.002)
	2-hour pp	$R = .667$ (.001)	$R = .220$ (NS)
C-Peptide	Fasting	$R = .657$ (.001)	$R = .660$ (.001)
	2-hour pp	$R = .502$ (.017)	$R = .091$ (NS)

NOTE. BMI was correlated by the Pearson correlation test. Pearson correlation' coefficient of 0.35 to 0.49 was interpreted empirically as low, 0.5 to 0.79 as moderate, and 0.8 or greater as high.

lin, as well as proinsulin levels, were significantly increased in the VPA group. The BMI values of both the VPA-treated and the control patients showed a significant positive correlation to the fasting levels of insulin, proinsulin, and C-peptide. A relationship of BMI with pp values was only found in the VPA group. To our knowledge, this observation of a possible relationship between VPA therapy and an increased pp insulin secretion is new and might add further information to the weight gain under VPA therapy.

Among the various mechanisms, how VPA might alter insulin secretion, neurotransmitters and their receptors also have to be considered.[34,35] In animals, gamma aminobutyric acid (GABA) receptor stimulation by GABA-ergic drugs, including benzodiazepine, caused membrane depolarization and insulin release.[36-38] The plasma levels of GABA were found to increase during VPA treatment, while tissue concentrations of GABA differ significantly, because VPA is not equally distributed in the body.[23,24] No data are available about VPA concentrations in the pancreatic tissue. Thus, in vitro studies will be necessary to define the possible mechanisms of how VPA modulates insulin secretion, stimulates appetite, and causes weight gain.

Previously published studies described that weight gain does not show a correlation with VPA plasma levels.[39] However, only few trials compared VPA with other antiepileptic drugs.[3,39] One publication compared VPA therapy with CBZ and oxcarbazepine and found a pronounced weight gain only in the VPA group.[40] While body weight did not increase during CBZ treatment in this publication,[40] other investigators reported a significant weight gain after add-on therapy with CBZ.[41] Data about a stable body weight during lamotrigine therapy[39,42] support the choice of lamotrigine as a control substance in our evaluation.

Another point of concern is the fact that most of the published studies about the metabolic effects of VPA included particularly female patients, because VPA therapy followed by increased insulin resistance might alter ovarian function.[5] Considering the effects of gender on body fat and leptin levels,[43] we have also performed our evaluation in a female population to obtain a comparable study design, but of course, studies in male patients will be necessary. The precise mechanisms underlying VPA-associated weight gain still remain unclear, and further studies on this topic seem to be of clinical importance with respect to weight-reducing and weight-maintaining therapeutic procedures.

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