Valproate, weight gain and carbohydrate craving: A gender study

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Summary
Purpose: To compare the incidence and magnitude of weight gain associated with valproic acid (VPA) monotherapy in male and female epilepsy patients and to determine possible gender-specific differences in frequency of carbohydrate craving, body-composition, glucose homeostasis and lipid metabolism.

Methods: Epilepsy patients on VPA monotherapy were consecutively recruited at the outpatient clinic of the Department of Neurology, Innsbruck Medical University. Weight gain during VPA-therapy, frequency of carbohydrate craving and physical exercise, sociopsychological problems and family history for diabetes were obtained from all patients. Clinical data also comprised body-impedance analysis, body mass index and waist-to-hip ratio. Morning fasting blood samples were drawn to determine serum leptin, glucose and lipid concentrations, as well as insulin, C-reactive protein and TNF-α.

Results: One hundred and six patients (55 women) were enrolled in the study. Significant weight gain was seen during VPA-therapy in both genders (each p < 0.001) with women experiencing increment of weight more frequently and more pronounced than did men. Analyses of patients who gained weight during VPA-therapy revealed significantly higher serum leptin concentrations in women than in men (p < 0.001). Women also revealed significantly higher high-density lipoprotein-cholesterol and lower triglyceride concentrations than men (p = 0.004 and 0.014, respectively). Frequency of carbohydrate craving was 25.8% in women and 14.3% in men. More women tried to lose or control weight through diet than did men (22.6%...
Introduction

Valproic acid (VPA) has a broad spectrum of anticonvulsant activity, being at present the antiepileptic drug (AED) of choice for all forms of generalized epilepsy and has become established worldwide as one of the most widely prescribed AEDs. However, weight gain as the most common side-effect of VPA<sup>3</sup>—5 limits its use in clinical practice more often than do other possible idiosyncratic side-effects and high rates of teratogenicity. VPA-related weight gain was found to be frequent in women with epilepsy, increasing the possibility for metabolic disturbances. Verrotti et al. reported the development of obesity in 37% of female patients with epilepsy after 1 year of treatment with VPA. Weight gain due to VPA treatment is usually observed during the first 3 months of therapy,<sup>7</sup>—11 reaching its maximum after 6 months.<sup>3,4,12,13</sup>

Consequences of VPA-associated weight gain are the risk for developing non-alcoholic fatty liver disease (NAFLD)<sup>14</sup> and insulin resistance (IR).<sup>4,15,16</sup> Furthermore, it is well established that weight gain and obesity are associated with an increase in patients’ cardiovascular risk<sup>17</sup> and increased non-compliance or therapy interruption.<sup>12,13,18</sup>

Up to now, attempts to determine factors responsible for VPA-induced weight gain failed. Several mechanisms have been proposed: (i) ineffective leptin action despite high leptin levels,<sup>5,20,21</sup> (ii) hyperinsulinemia resulting from increased secretion of β-cells<sup>22</sup> and (iii) increased consumption of food and energy-rich drinks due to increased appetite (e.g. carbohydrate craving) and modified thirst.<sup>3,13</sup>

VPA treatment in humans is known to increase the serum level of two hormones, leptin<sup>6,20,21</sup> and insulin,<sup>23</sup> produced by adipose tissue and the pancreatic islet cells,<sup>22</sup> respectively. One of the physiologic roles of leptin is an appetite-reducing feedback signal.<sup>24</sup> In humans, serum leptin and insulin concentrations are associated with the amount of adipose tissue and are higher in obese than in lean people.<sup>25,26</sup> In epilepsy patients, higher serum leptin as well as insulin concentrations in overweight females compared to males<sup>15</sup> have been demonstrated.

To date, the etiology of VPA-induced weight gain is considered to be multi-factorial since weight is the output of energy homeostasis controlled by many organs that produce and secrete a variety of appetite-regulating peptides and cytokines that act within the hypothalamus.<sup>27</sup>

The aims of this study were to elucidate possible effects of gender on the magnitude of VPA-associated weight gain, carbohydrate craving and disturbances in body-composition, glucose and lipid homeostasis.

Methods

One hundred and twenty patients (61 women and 59 age matched men) were consecutively recruited from our outpatient clinic, presenting with either partial or generalized epilepsy treated with VPA monotherapy for at least 6 months. None of the patients had any other regular medication in addition to VPA. Patients with a mental handicap, with a history of psychogenic seizures and/or concomitant diseases possibly contributing to weight gain were excluded.

All patients underwent standardized questionnaire about family history of diabetes, the magnitude of weight gain under VPA therapy, eating habits, especially carbohydrate craving, sociopsychological burden of weight gain and physical exercise at the time of investigation. Each patient was measured for weight, height, hips and waist using a wall-mounted stadiometer, a tape measure and a calibrated weight scale, respectively, with subjects wearing underwear only.

Body-impedance analysis and fasting blood samples were obtained in all patients fulfilling the inclusion criteria between 8 and 10 in the morning. Each sample of whole blood was centrifuged to obtain serum, which was immediately frozen at −80°C within 1 h after sampling, and stored in aliquots until the assays were run. Additionally, baseline anthropometric data from 1 day before VPA treatment was obtained from the patients’ record (“initial weight”).

Body impedance as an expression of body fat portion was measured with a body fat monitor (OMRON BF 302), which measures the percentage and total amount of fat in kilograms contained in the human body. It analyses the electrical resistance of
the body tissues by sending a weak electrical current through the upper body. Body fat was classified in categories according to Deurenberg et al. as thin, normal, stout, obese and extremely obese in men/women (<10/<20%), (10—20/20—30%), (20—25/30—35%), (25—30/35—40%), (>30/>40%).

Glucose was measured with an automated hexokinase method (HK, Uni-Kit III, Roche, Basle, Switzerland; RIA-mat, C-peptide II, Byk-Sangtec Diagnostica, Germany). Serum free insulin and C-peptide were determined with radioimmunoassay (RIA, Pharmacia, Uppsala), and proinsulin with an enzyme immunoassay (Mercodia, Uppsala, Sweden). High-sensitive C-reactive protein was determined with use of the CRP (Latex) ultrasensitive assay (Roche, Vienna, Austria). Tumor-necrosis-factor-alpha was measured with TNF-α EASIA (Biosource, Belgium).

Plasma leptin concentrations were measured with an enzyme-linked immunosorbent assay (R&D System, Wiesbaden, Germany).

The homeostasis model assessment (HOMA) index for insulin resistance (HOMA-IR) as a measure for insulin resistance was calculated as fasting glucose (mmol/l) × fasting serum insulin (µU/ml)/22.5.

Plasma lipids, thyroid, liver and kidney function test were determined according to routine procedures.

Statistical analysis was performed using SPSS software; p values less than 0.05 were considered significant. Items used include the Chi-square test, T-test, Pearson and Spearman correlation coefficient.

Results

All of 120 patients agreed to participate in the study and attended the interview. Six patients did not attend blood sampling session, eight patients’ initial weight was not documented. Therefore, 106 patients (55 women and 51 age-matched men; Table 1) were included in our study. Baseline characteristics and main results are presented in Table 1.

The mean duration of VPA treatment was 1.5 ± 0.7 years in women and 1.8 ± 0.5 years in men, demonstrating no significant difference (p = 0.530). VPA dosages were similar in both groups, no significant difference in seizure type distribution was seen between genders (Table 1). Significant weight gain was seen during VPA-therapy in both genders (each p < 0.001) with women experiencing increment of weight more frequently and more pronounced than did men (Tables 1 and 2). A high portion of patients in both genders who gained weight during VPA-therapy faced significant weight gain of >5 kg (Table 2). Although mean BMI at baseline was significantly different between women and men (p = 0.031), an almost identical mean BMI was seen at follow up (p = 0.659; Table 1). 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 (27.5 ± 6.9% versus 18.7 ± 7.1% and 0.79 ± 0.05 versus 0.91 ± 0.07, respectively). Serum leptin concentration was significantly higher in women than in men (18.0 ± 12.5 mg/ml versus 5.0 ± 4.1 mg/ml, p < 0.001). Women also revealed significantly higher HDL-cholesterol concentrations than men (62.5 ± 17.4 mg/dl versus 48.8 ± 11.7 mg/dl, p < 0.001). Parameters of glucose homeostasis and inflammation did not reveal any differences.

Additional analyses were performed in patients who gained weight during VPA-therapy.

Comparison of women and men who gained weight during VPA-therapy showed statistically different waist-to-hip ratio and percentage of body fat.
fat between men and women, with women expressing higher percentage of body fat and a lower waist/hip ratio (Table 2).

Frequency of carbohydrate craving was 25.8% in women and 14.3% in men. Reported sport activities did not differ between both genders. However, more women than men tried to lose or control weight by diet (22.6% versus 7.1%). Moreover, weight gain as a sociopsychological problem was more pronounced in women than in men (54.8% versus 21.4%). There was no difference in the frequency of diabetes in families of men or women (Table 2).

Serum leptin concentration was significantly higher in women than in men ($p < 0.001$) who gained weight during VPA-therapy. Women also revealed significantly higher HDL-cholesterol concentrations and lower triglyceride concentrations than men ($p = 0.004$ and 0.014, respectively; Table 3).

Fasting plasma glucose, insulin, pro-insulin and C-peptide as well as the HOMA-IR did not differ significantly between men and women (Table 3). Interestingly, two parameters associated with the inflammatory aspect of obesity, namely TNF-$\alpha$ and CRP, did not show any statistical difference between genders (Table 3).

### Discussion

The present study demonstrates a more pronounced and more frequent weight gain in women receiving VPA monotherapy compared to men. VPA treatment was associated with various degrees of weight gain (mild, moderate or excessive) for both genders, with incidences comparable to prior studies.7,11,30–32

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**Table 2** Anthropometric data and other information of subjects who gained weight under VPA

<table>
<thead>
<tr>
<th></th>
<th>Women ($n = 31$)</th>
<th>Men ($n = 14$)</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average weight gain (kg)</td>
<td>8.8 ± 7.0</td>
<td>7.9 ± 4.4</td>
<td>0.949</td>
</tr>
<tr>
<td>Significant weight gain (&gt;5 kg; %)</td>
<td>43.6</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>Average significant weight gain (kg)</td>
<td>13.4 ± 7.1</td>
<td>10.5 ± 4.0</td>
<td>0.299</td>
</tr>
<tr>
<td>Carbohydrate craving attacks (%)</td>
<td>25.8</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>Physical activity (%)</td>
<td>22.6</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Dietary regimens (%)</td>
<td>64.5</td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>Family history of diabetes (%)</td>
<td>34.5</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td>Initial BMI</td>
<td>22.9 ± 4.0</td>
<td>24.7 ± 3.7</td>
<td>0.156</td>
</tr>
<tr>
<td>Follow-up BMI</td>
<td>26.1 ± 3.5$^a$</td>
<td>27.2 ± 3.6$^a$</td>
<td>0.361</td>
</tr>
<tr>
<td>Waist/hip ratio average</td>
<td>0.79 ± 0.05</td>
<td>0.93 ± 0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>6.4% (&gt;0.85)</td>
<td>7.1% (&gt;1)</td>
<td></td>
</tr>
<tr>
<td>Body fat (% of body weight)</td>
<td>22.5% (&gt;35%)</td>
<td>21.4% (&gt;25%)</td>
<td></td>
</tr>
<tr>
<td>Body fat average (%)</td>
<td>29.8 ± 6.7</td>
<td>21.1 ± 6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight gain as a sociopsychological problem (%)</td>
<td>54.8</td>
<td>21.4</td>
<td></td>
</tr>
</tbody>
</table>

$n$, number of subjects; values are absolute numbers and percentage or means ± S.D. BMI, body-mass index.

$^a p < 0.001$ when compared with initial BMI.

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**Table 3** Metabolic and inflammatory parameters of patients who gained weight under VPA

<table>
<thead>
<tr>
<th></th>
<th>Women ($n = 31$)</th>
<th>Men ($n = 14$)</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin (ng/ml)</td>
<td>23.1 ± 13.1</td>
<td>6.7 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>12.2 ± 11.7</td>
<td>15.2 ± 12.4</td>
<td>0.444</td>
</tr>
<tr>
<td>Proinsulin (pmol/l)</td>
<td>15.5 ± 24.2</td>
<td>31.7 ± 60.2</td>
<td>0.208</td>
</tr>
<tr>
<td>C-peptide (pmol/ml)</td>
<td>0.73 ± 0.33</td>
<td>0.95 ± 0.46</td>
<td>0.080</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>74.8 ± 24.5</td>
<td>89.4 ± 29.3</td>
<td>0.104</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>2.4 ± 3.3</td>
<td>4.0 ± 4.6</td>
<td>0.189</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>200.2 ± 39.2</td>
<td>209.0 ± 28.5</td>
<td>0.455</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>60.9 ± 19.4</td>
<td>44.0 ± 10.5</td>
<td>0.004</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>113.8 ± 38.6</td>
<td>133.8 ± 22.2</td>
<td>0.100</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>127.1 ± 64.00</td>
<td>195.4 ± 113.3</td>
<td>0.014</td>
</tr>
<tr>
<td>Lipoprotein (a) (mg/dl)</td>
<td>29.2 ± 32.1</td>
<td>40.9 ± 37.3</td>
<td>0.315</td>
</tr>
<tr>
<td>TNF-$\alpha$ (pg/ml)</td>
<td>19.7 ± 20.2</td>
<td>14.0 ± 5.3</td>
<td>0.162</td>
</tr>
<tr>
<td>High-sensitive C-reactive protein (mg/dl)</td>
<td>0.39 ± 0.52</td>
<td>0.23 ± 0.33</td>
<td>0.492</td>
</tr>
</tbody>
</table>

$n$, number of subjects; values are absolute numbers and percentage or means ± S.D. HOMA index, homeostasis model assessment index for insulin resistance; TNF-$\alpha$, tumor-necrosis-factor alpha; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
Different mechanisms, such as an increased consumption of food and energy-rich drinks due to increased appetite (e.g., carbohydrate craving) and modified thirst, were proposed to explain the weight modifying effect of VPA therapy. Carbohydrate craving is a frequently observed phenomenon in patients with affective disorders. However, the proximate mechanisms for increased intake have not been identified yet. Carbohydrate craving has been attributed to central serotonin depletion and is felt to be a macronutrient-specific appetite. This is the first study showing carbohydrate craving to be a common side-effect predominantly in women undergoing VPA-therapy. In patients undergoing VPA-therapy this might be possibly related to postprandial insulin secretion recently described. Furthermore, sociopsychological burden of women experiencing weight gain due to VPA therapy is higher compared to men, resulting in increased non-compliance and therapy-interruption.

Other possibly involved mechanisms in VPA-associated weight gain include defective sympathetic nervous system activity, modulation on a genetic basis for obesity, carnitine deficiency causing impaired beta-oxidation of fatty acids, ineffective leptin action despite high leptin levels (leptin-resistance) and hyperinsulinemia resulting from increased secretion of insulin. Beside its function as energy storage, adipose tissue acts as an endocrine organ by releasing various factors into the circulation. The so-called adipocytokines (e.g., leptin, adiponectin) have recently been defined as a link between increased body weight and the development of insulin resistance. Leptin is a key homeostatic regulator of body weight and energy expenditure. As previously reported, serum leptin levels were higher in female than in male overweight epilepsy patients, possibly leading to leptin-resistance. In accordance, women revealed a higher percentage of body fat paralleled by higher plasma leptin levels compared to men in this study.

To us, however, this finding by itself does not account for the higher incidence of weight gain in women solely. The question whether leptin overproduction is one of the causes or consequences of obesity has not even settled. The diverse mechanisms linking leptin to the brain and peripheral tissues might clarify the pathogenesis of obesity and associated diseases.

Interestingly, female patients showed lower fasting triglycerides and increased HDL-cholesterol values compared to men, indicating a higher degree of insulin sensitivity. This might be due to a higher percentage of women trying to lose weight by dietary procedures resulting in a more favorable lipid composition. Only recently, visceral fat mass has been found to be a major correlate of diabetogenic, atherogenic, prothrombotic and proinflammatory metabolic abnormalities referred to as the metabolic syndrome. A moderate weight loss in abdominally obese patients is associated with substantial improvements in the metabolic profile.

In this study, waist/hip ratios were different in both sexes reflecting different physiological and constitutional attributes of men and women. Interestingly, both genders showed a similar rate of elevated waist/hip ratios, indicating similar metabolic burden through an increase in visceral fat mass.

Additionally to adipocytokines, adipose tissue secretes various markers of subclinical inflammation (e.g., C-reactive protein, TNF-). It is well established, that subclinical inflammation is related to the development of insulin resistance, type 2 diabetes and increased cardiovascular risk. Unexpectedly, plasma levels of C-reactive protein and TNF- did not differ between lean and overweight patients as well as between men and women who gained weight under VPA treatment.

Long-term VPA treatment and weight gain are frequently associated with the development of hyperinsulinemia, suggesting development of insulin resistance.

Some authors suggest an association between hyperinsulinemia and various endocrine abnormalities, possibly stimulating the ovaries to overproduce androgens causing hirsutism and metabolic disorders. In detail, insulin inhibits the production of the hepatic synthesis of insulin-like growth factor 1 binding protein (IGFBP-1), which might lead to increased bioactive insulin-like growth factor 1 (IGF-1) levels. Despite insulin resistance in adipose and muscular tissue, the ovaries remain insulin sensitive and as a result, insulin as well as IGF-1 still exerts stimulatory effects on the ovaries. These effects include theca cell hyperplasia and consequently increased production of androgens. Despite the higher percentage of weight gain in women, as well as the higher percentage of body fat paralleled by higher plasma leptin levels, we could not find significant differences in serum fasting glucose, serum insulin concentrations or HOMA-IR between men and women undergoing VPA therapy.

Unfortunately, predictors of weight gain due to VPA therapy have not yet been identified. Contradictory results were reported for variables such as baseline weight and BMI, gender, valproate dose, seizure or epilepsy type and neurocognitive status.
weight gain problems are more common in patients with psychogenic seizures.\textsuperscript{58} In addition, patients with generalized versus partial seizures\textsuperscript{11} and those with normal versus abnormal neurocognitive status\textsuperscript{58} tend to be at greater risk for an increase in weight. To rule out conflicting data, no patients with psychogenic seizures or abnormal neurocognitive status were included in this study. We did not find any difference in incidence of weight gain between generalized and partial epilepsy patients.

In conclusion, our evaluation demonstrates gender disparities in weight modifying effects of valproate in epilepsy patients. Women are more prone to gain weight during VPA therapy than men. This might possibly be related to leptin-resistance or high frequency of carbohydrate craving. Because sociopsychological burden of women experiencing weight gain due to VPA therapy is high, prevention and therapeutic approaches should focus on women and include strategies against carbohydrate craving.

References
