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Serum Insulin, Cortisol, Leptin, Neuropeptide Y, Galanin and Ghrelin Levels in Epileptic Children Receiving Valproate

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Key Words
Valproate · Weight gain · Leptin · Neuropeptide Y · Galanin · Ghrelin

Abstract
Aims: The objective of this study was to investigate the cause of valproate (VPA)-associated weight gain in children. ***Methods:*** Eighteen children (10.94 ± 3.78 years) with epilepsy were assigned to VPA therapy. Serum levels of glucose, insulin, cortisol, leptin, neuropeptide Y (NPY), galanin and ghrelin were assessed before (month 0) and after 18 months of therapy. Eighteen age- and gender-matched patients (10.78 ± 3.95 years) were enrolled as the control group. ***Results:*** Excess per capita weight of 2.3 kg was determined in the children receiving VPA over 18 months compared to the control group. In these patients, a statistically significant increase in standardized weight score, Homeostasis Model Assessment index, serum leptin, NPY and galanin values was determined at the 18th month compared to those before VPA treatment and in the control group, and there was also a significant decrease in ghrelin values. ***Conclusion:*** Increased serum levels of leptin, NPY and galanin play an important role in VPA-associated weight gain in children. While ghrelin is not directly associated with weight gain, its serum levels decline as a response to weight gain.

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Introduction

Valproate (VPA) is a commonly employed broad-spectrum antiepileptic drug that is also being increasingly used for bipolar disorder and migraine prophylaxis [1–3]. Although it is regarded as well-tolerated and safe, weight gain is a common adverse effect of VPA therapy, occurring in up to 58% of children [4] and 71% of adult patients [5]. Weight gain in children due to VPA treatment is usually observed during the first 3 months of therapy [6, 7], reaching a maximum after 6–16 months [8, 9], though it may also be progressive [10]. Several mechanisms have been suggested in connection with VPA-induced weight gain, such as reduced physical activity [11], increased appetite [12], the effect of VPA on the hypothalamus [13], a decreased capacity for luxury consumption or facultative thermogenesis [12] and high cortisol [7], hyperinsulinemia and insulin resistance [14]. The discovery of leptin, neuropeptide Y (NPY) and also ghrelin has added a new perspective to the pathophysiology of VPA-induced weight gain. However, an association between VPA and increased [7, 15], decreased [16] or normal [17] leptin and increased [18, 19] or decreased [20] ghrelin and NPY [7] levels has been reported, though the results are still a matter for debate.

In order to further investigate the pathophysiology of VPA-induced weight gain in children with epilepsy, and

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for the first time in the same study, we prospectively analyzed circulating serum cortisol, Homeostasis Model Assessment (HOMA) index, insulin, leptin, NPY, ghrelin and galanin levels in such patients.

Patients and Methods

This study was conducted at the Gazi University Hospital Department of Pediatric Neurology with the approval of the Institutional Ethics Committees and in conformity with the Helsinki Declaration, International Conference on Harmonization/Good Clinical Practice and local regulations.

Study Participants

Eighteen (9 prepubertal, 9 pubertal) pediatric patients (age range 3.4–15.8 years) newly diagnosed with idiopathic partial and generalized epilepsy were enrolled. Eighteen age- and gender-matched patients (9 prepubertal, 9 pubertal; age range 3.5–16 years) were enrolled as the control group. Control subjects and patients not on antiepileptic drugs or any other drugs that might affect weight metabolism (e.g. steroids or multivitamin preparations), who were ambulatory, without any neurological deficit or underlying renal, hepatic, endocrine, cardiac, neurometabolic or any other chronic diseases were included. Description of seizure types followed the criteria set out by the International League Against Epilepsy [21]. The antiepileptic drug dose used was selected according to generally accepted guidelines [22]. VPA was administered twice a day.

Two initially recruited patients were excluded for social reasons, 2 due to another disease affecting weight gain and 5 because a second antiepileptic drug had to be added to treat their persistent epileptic attacks. Antiepileptic drugs were administered twice a day. Eventually, a total of 18 epileptic patients were evaluated.

Written informed consent was obtained from each patient and/or parents. The study was approved by the Gazi University Faculty of Medicine Ethics Committee.

Methods

Each patient and control subject was clinically examined by one of the authors at baseline (month 0) and at 18 months. Weight, serum blood sugar, cortisol, insulin, leptin, HOMA index [fasting glucose (mmol/l) × fasting insulin (mIU/l)/22.5], NPY, galanin and ghrelin were evaluated at baseline and 18 months in all patients. Hand-wrist radiographs were evaluated for bone maturation. The pubertal status of the patients was assessed according to the method described by Marshall and Tanner [23, 24]. Neyzi's growth and development charts for Turkish children were used for the evaluation of height and weight [25, 26]. Weighted standard deviation scores were calculated according to the Turkish child population [27, 28]. The body mass index (BMI) of each patient was calculated at each follow-up by weighing the subjects on a standard scale and measuring their height in bare feet.

Blood samples for the analysis of serum glucose, insulin, cortisol, leptin, NPY and galanin levels were obtained between 8.00 and 8.30 a.m. after overnight fasting. After the sera had been separated within 1 h, the samples were kept at –70°C until assayed.

Serum Sample Assay

Glucose was measured in our hospital's central laboratory using kits from the Biosystems Reagent and Instruments Company with enzymatic spectrophotometric glucose oxidase/peroxidase. Insulin was investigated at the Gazi University Nuclear Medicine Laboratory using a DPC-Immulite 2000 autoanalyzer based on enzyme substrate connection using an insulin kit (catalogue number L2KIN2, Diagnostic Products Corporation, Los Angeles, Calif., USA). Cortisol was investigated at the Gazi University Nuclear Medicine Laboratory with a DPC-Immulite 2000 autoanalyzer. Leptin was investigated at the Gazi University Pediatric Endocrinology Laboratory using a DSL kit. Outcomes were evaluated using an I^{125}-marked Berthold LB 2111 device at intervals of 0.25–120 ng/ml. NPY was investigated at the Gazi University Pediatric Endocrinology Laboratory using a Phoenix Pharmaceuticals kit and the RIA method. Outcomes were evaluated using a I^{125}-marked Berthold LB 2111 device at standard intervals of 1–128 pg/ml. Serum galanin and ghrelin levels were measured using a commercial RIA kit (Ghrelin human RIA kit, Phoenix Pharmaceuticals Inc., Belmont, Calif., USA), and samples for quality control were included in each assay.

Blood samples were anticoagulated with EDTA and aprotinin, kept on ice and centrifuged at 1,800 *g* for 15 min.

Serum concentrations of VPA were analyzed using the fluorescence polarization method on an AxSym analyzer (Abbott Diagnostic Division, Irving, Tex., USA).

Measurement Analysis

Once the results had been finalized, body weight, BMI, fasting serum glucose, cortisol, insulin, HOMA index, leptin, NPY and galanin levels in cases and controls at baseline (month 0) and 18 months were investigated.

Statistical Analysis

Data analysis was performed using SPSS 11.5. Descriptive statistics are shown as means ± SD. Compatibility of constant variables with normal distribution was tested using the Shapiro-Wilk test. The dependent t test or Wilcoxon signed rank test was used to test for statistical significance among repeated measurements. Treatment (month 0 and 18th month) and control groups were compared in terms of basic characteristics. Student's t test or the Mann-Whitney U test was used to test for statistically significant differences among repeated measurements. The significance of the linear correlation between treatment-associated changes in BMI and insulin levels in the VPA group was examined using the Spearman correlation test. Significance was set at $p < 0.05$. Analysis of correlation between the analyzed hormones before and after treatment (delta of variation) was performed using Pearson's correlation coefficient. A p value less than 0.05 was considered statistically significant.

Results

The clinical characteristics of the patients and control group are summarized in table 1.

Average baseline weight in the control group was 39.95 ± 15.03 kg, compared to 44.82 ± 15.93 kg at 18 months,

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Table 1. Clinical characteristics of the VPA-treated patients and control group

	n	Age, years	VPA dose			Epilepsy type			Pubertal stage		VPA level, μg/ml	
			20 mg/kg/day	25 mg/kg/day	30 mg/kg/day	P	G	SG	prepubertal	pubertal	3rd month	18th month
VPA	18	10.94 ± 3.78	2	10	6	6	5	7	10	8	75.04 ± 13.66	71.17 ± 24.6
Control	18	10.78 ± 3.95							11	7		

Values represent numbers of patients, except where indicated otherwise. P = Idiopathic localization-related epilepsy; G = idiopathic generalized epilepsy; SG = secondary generalized epilepsy.

a difference of approximately 5 kg (1.3–9.9 kg). In the VPA group, baseline weight was 38.72 ± 15.10 kg, and at 18 months it was 46.0 ± 16.34 kg, a difference of approximately 7.3 kg (0.56–17.70 kg). After 18 months, the cases in the VPA group had gained an average 2.3 kg more than the control group.

A statistically significant increase was observed in standardized weight score (standard deviation score), BMI, HOMA index, leptin, NPY, galanin and ghrelin values after 18 months of treatment in the VPA group compared to before treatment (baseline, month 0). A statistically significant increase was observed in BMI, leptin, NPY, galanin and ghrelin values after 18 months of treatment in the VPA group compared to the control group ($p < 0.05$). There was no difference in serum glucose, insulin or cortisol levels between 18 months and baseline in controls ($p > 0.05$). Weighted standard deviation, BMI, glucose, cortisol, insulin, HOMA index, leptin, NPY, galanin and ghrelin levels for the controls and VPA patients are shown in table 2.

No delta correlation was determined between hormones in the control group ($p > 0.05$), though in the VPA group a good correlation was established between insulin and leptin ($r = 0.72$; $p < 0.001$) and a weak to medium correlation between leptin and NPY ($r = 0.48$; $p < 0.045$). The correlations between the hormones before and after treatment (delta of variation) in the control and VPA cases are summarized in table 3.

Baseline and 18-month values of all parameters in the 9 cases who gained more than the expected 2.5 kg were compared with those who gained less using the Spearman correlation test, which revealed significance for insulin alone. There was a significant correlation in terms of insulin values in the cases who gained more than the expected 2.5 kg ($r = 0.69$; $p = 0.04$; data not shown).

Discussion

This study demonstrates that VPA causes weight gain and changes in circulating levels of leptin, NPY, galanin and ghrelin in children.

VPA-associated weight gain was first determined in 1981 by Egger and Brett [29], in a study in which 44 out of 100 children using VPA gained weight. It has since been reported in a considerable number of other studies, and VPA therapy is associated with weight gain in both adults [30] and children [30]. In adults, the reported frequency of significant weight gain, commonly defined as 4 kg or more, is between 57 and 70% [5, 31–33]. An open-label, 24-week, randomized study comparing lamotrigine, carbamazepine and VPA in patients newly diagnosed with epilepsy (n = 239) determined weight gain only in the VPA-treated patients, with a mean weight increase of 3.9 kg [34]. Privitera et al. [35] reported that, as in adult patients, VPA causes a mean weight gain of between 2.0 and 5 kg in children. We also report a mean weight gain of more than 2.3 kg after 18 months of treatment in epileptic children using VPA compared to controls of the same age and gender. In contrast to adults, the incidence of significant weight gain in childhood varies between studies [36, 37]. These have reported that VPA treatment does not cause weight gain in pubertal or prepubertal children.

Insulin and leptin are the key neuropeptides recognized by the brain for regulation of food intake and energy expenditure [38]. Insulin and leptin concentrations increase after weight gain and correlate with the extent of that gain. It has been suggested that VPA-associated weight gain may be associated with high concentrations of serum insulin and leptin [7, 15]. In many studies [30, 31], though not all [16, 17], high insulin and leptin have been determined in cases with VPA-associated weight

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Table 2. Body weight, BMI and glucose, cortisol, insulin, leptin, NPY, galanin and ghrelin levels in the control and VPA-treated cases

Variable	Control		VPA	
	month 0	18th month	month 0	18th month
WDS				
Prepubertal (n = 9)	0.56 ± 0.88	0.64 ± 1.42	0.34 ± 1.28	0.75 ± 1.68
Pubertal (n = 9)	–0.28 ± 0.49	–0.13 ± 0.89	–0.56 ± 1.02	0.38 ± 0.63
Total (n = 18)	0.09 ± 0.80	0.21 ± 1.19	–0.10 ± 1.13	0.57 ± 1.25[c]
Weight, kg				
Prepubertal (n = 9)	26.31 ± 7.33	30.80 ± 8.43	24.70 ± 5.52	31.45 ± 7.12
Pubertal (n = 9)	51.89 ± 7.53	57.04 ± 8.67	52.75 ± 3.51	60.56 ± 6.32
Total (n = 18)	39.95 ± 15.03	44.80 ± 15.9	38.7 ± 15.11	46.0 ± 16.34
BMI				
Prepubertal (n = 9)	16.67 ± 1.81	17.42 ± 1.74	15.90 ± 2.25	17.84 ± 2.01
Pubertal (n = 9)	19.19 ± 1.87	20.34 ± 2.34	19.69 ± 0.64	21.72 ± 1.47
Total (n = 18)	18.01 ± 2.20	18.84 ± 2.49	17.8 ± 2.52	19.8 ± 2.63[c, x]
Glucose, mg/dl				
Prepubertal (n = 9)	90.38 ± 5.15	90.50 ± 6.02	87.8 ± 5.83	86.8 ± 7.10
Pubertal (n = 9)	87.30 ± 6.36	84.50 ± 7.14	87.3 ± 5.17	86.8 ± 6.11
Total (n = 18)	88.7 ± 5.90	87.1 ± 7.13	87.6 ± 5.34	86.8 ± 6.43
Cortisol, μg/dl				
Prepubertal (n = 9)	14.43 ± 5.67	12.46 ± 3.24	13.0 ± 4.51	14.8 ± 5.84
Pubertal (n = 9)	12.88 ± 4.24	13.74 ± 4.44	12.5 ± 6.49	11.8 ± 3.10
Total (n = 18)	13.57 ± 4.85	13.12 ± 5.74	12.8 ± 5.42	13.29 ± 4.80
Insulin, μU/ml				
Prepubertal (n = 9)	5.27 ± 2.17	6.22 ± 3.71	6.54 ± 4.79	9.47 ± 4.84
Pubertal (n = 9)	7.72 ± 3.40	6.10 ± 4.18	6.65 ± 3.34	6.73 ± 3.03
Total (n = 18)	6.63 ± 3.10	6.12 ± 4.36	6.60 ± 4.01	8.10 ± 4.16
HOMA index				
Prepubertal (n = 9)	1.17 ± 0.51	1.36 ± 0.79	1.31 ± 0.93	1.50 ± 0.52
Pubertal (n = 9)	1.65 ± 0.75	1.29 ± 1.01	1.55 ± 0.93	1.95 ± 1.15
Total (n = 18)	1.44 ± 0.68	1.32 ± 0.89	1.43 ± 0.91	1.73 ± 0.90[a]
Leptin, ng/ml				
Prepubertal (n = 9)	8.89 ± 3.86	8.33 ± 4.72	9.00 ± 2.49	12.73 ± 3.06
Pubertal (n = 9)	9.10 ± 1.61	7.90 ± 2.30	9.43 ± 2.56	11.03 ± 4.40
Total (n = 18)	9.01 ± 2.75	8.05 ± 3.06	9.22 ± 2.56	11.88 ± 3.78[b, x]
NPY, pg/ml				
Prepubertal (n = 9)	27.64 ± 5.36	26.70 ± 4.21	21.66 ± 4.19	30.31 ± 4.60
Pubertal (n = 9)	23.81 ± 5.46	23.09 ± 4.62	25.01 ± 5.36	30.07 ± 4.64
Total (n = 18)	25.51 ± 5.61	24.78 ± 4.94	22.33 ± 4.98	30.19 ± 4.48[c, y]
Galanin, pg/ml				
Prepubertal (n = 9)	4.64 ± 1.82	4.00 ± 0.71	4.38 ± 1.62	7.56 ± 1.92
Pubertal (n = 9)	5.60 ± 1.45	5.71 ± 1.17	5.80 ± 2.04	5.82 ± 1.52
Total (n = 18)	5.17 ± 1.65	4.94 ± 1.98	5.09 ± 1.93	6.69 ± 1.90[a, x]
Ghrelin, pg/ml				
Prepubertal (n = 9)	327.8 ± 92.43	300.1 ± 79.83	361.3 ± 81.59	262.8 ± 114.5
Pubertal (n = 9)	359.5 ± 106.0	358.6 ± 87.72	347.0 ± 57.98	261.3 ± 77.5
Total (n = 18)	345.0 ± 98.4	332.8 ± 87.5	354.7 ± 70.71	262.5 ± 94.27[c, z]

Values are expressed as means ± SD. WSD = Weighted standard deviation. [a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$: significantly different compared to baseline values in VPA-treated patients (dependent t test or Wilcoxon signed rank test). [x] $p < 0.05$, [y] $p < 0.01$, [z] $p < 0.001$: significant difference between baseline values in controls and baseline and 18-month values in VPA patients (Student's t test or the Mann-Whitney U test).

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Table 3. Evaluation of correlations between the analyzed hormones before and after treatment (delta of variation) in the control and VPA-treated cases

	Cortisol (μg/dl)		Insulin (μU/ml)		Leptin (ng/ml)		NPY (pg/ml)		Galanin (pg/ml)	
	r	p	r	p	r	p	r	p	r	p
Control										
Insulin	–0.08	0.738								
Leptin	–0.03	0.913	0.34	0.174						
NPY	0.20	0.418	–0.28	0.267	–0.04	0.868				
Galanin	0.13	0.604	–0.20	0.437	0.17	0.489	0.07	0.798		
Ghrelin	–0.43	0.075	0.31	0.903	0.38	0.880	–0.12	0.651	0.19	0.443
VPA										
Insulin	0.23	0.358								
Leptin	0.43	0.072	0.72	0.001						
NPY	0.25	0.311	0.33	0.185	0.48	0.045				
Galanin	0.30	0.226	0.45	0.063	0.40	0.098	0.04	0.887		
Ghrelin	0.35	0.150	0.29	0.247	0.35	0.154	0.24	0.341	0.05	0.855

gain. Verrotti et al. [14] showed 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 also demonstrated that after 18 months of VPA treatment, weight gain patients had significantly higher serum insulin (especially in those cases who gained more than 2.5 kg) and leptin levels. We also showed a powerful correlation between insulin and leptin increase in weight gain cases. The high insulin and leptin in our patients may also be the result of weight gain, due to their increased production by the pancreatic B cells and adipose tissue, respectively. VPA may indirectly enhance insulin resistance by suppressing insulin-mediated peripheral glucose uptake [14].

Leptin action in the hypothalamus with regard to regulation of food intake and body weight is known to be mediated by orexigenic signals, such as NPY and galanin [39]. Stanley et al. [40] reported that chronic administration of NPY in the lateral ventricle or direct injection into the paraventricular nucleus in rats leads to weight gain, increased food intake and ultimately to obesity. They suggest that NPY is directly associated with weight increase, considering its direct appetite-enhancing effect. These results have similarly been demonstrated in several experimental and genetic models of obesity [41, 42]. In the first study investigating NPY levels in epileptic patients, Aydın et al. [7] observed that these had increased in the 3rd and 6th months after VPA treatment compared to baseline values. Brill et al. [43] reported that chronic administration of VPA to rats increased the amount of NPY mRNA in the hippocampus and elevated NPY protein expression by 30–50%, whereas VPA administered in a single dose had no such effect. Of the orexigenic neuronal systems, in addition to NPY, galanin may also potentially be implicated in mediating leptin action in the hypothalamus [39]. We determined a significant correlation between NPY and leptin increase, though not between leptin and galanin, in the weight gain cases in our study. Galanin is known to reduce energy consumption at the peripheral level and sympathetic activity of brown fat tissue and to increase fat intake [44, 45]. In the literature investigating the relationship between galanin and antiepileptics, Shi et al. [46] measured plasma levels of galanin in 61 epileptic children receiving topiramate for 4 months and 16 healthy controls receiving no treatment. They reported that while galanin levels were significantly low in children with decreased appetite posttreatment, there was no significant difference in those subjects without decreased appetite. In our investigation of the effects of VPA treatment on levels of NPY and galanin, we observed a significant difference in NPY and galanin levels between both values in patients at baseline (month 0) and the control group and values in patients at 18 months. We determined increased serum NPY and galanin levels with VPA treatment. These results suggest that weight gain during VPA treatment may be related to NPY and galanin levels.

Ghrelin is a 28-amino-acid peptide hormone produced mainly in the stomach fundus and is the most potent appetite-stimulating hormone emanating from the

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gastrointestinal tract [42]. Ghrelin is generally upregulated under conditions of negative energy balance and downregulated in a positive energy balance setting [47]. Greco et al. [19] reported that ghrelin is downregulated in human VPA-induced obesity. Prodam et al. [18] also reported reduced ghrelin levels in normal-weight epileptic prepubertal children under treatment with carbamazepine or VPA compared to healthy age- and weight-matched subjects. In contrast to these studies, Gungor et al. [20] reported increased ghrelin levels in 35 epileptic children treated with VPA. They suggested that VPA-related weight gain may be associated with an increase in ghrelin level in the early treatment period. Our study does not support this view, because we demonstrated that VPA reduced ghrelin levels in weight gain cases. A reduced ghrelin level may be a consequence of increased insulin or leptin, because ghrelin levels are correlated with fasting plasma levels of these hormones [19].

In conclusion, this study shows that 18 months of VPA treatment in children led to a weight gain greater than the 2.3 kg to be expected in children of comparable age and sex. Insulin, leptin, NPY and galanin levels rose in the cases using VPA, while ghrelin levels declined. VPA-associated weight gain may be correlated with increased insulin, leptin and NPY and decreased ghrelin values.

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References

1 Davis R, Peters DH, McTavish D: Valproic acid. A reappraisal of its pharmacological properties and clinical efficacy in epilepsy. Drugs 1994;47:332–372.
2 Smith LA, Cornelius VR, Azorin JM, Perugi G, Vieta E, Young AH, Bowden CL: Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. J Affect Disord 2010;122:1–9.
3 Klapper J: Divalproex sodium in migraine prophylaxis: a dose-controlled study. Cephalalgia 1997;17:103–108.
4 Wirrell EC: Valproic acid-associated weight gain in older children and teens with epilepsy. Pediatr Neurol 2003;28:126–129.
5 Corman CL, Leung NM, Guberman AH: Weight gain in epileptic patients during treatment with valproic acid: a retrospective study. Can J Neurol Sci 1997;24:240–244.
6 Demir E, Aysun S: Weight gain associated with valproate in childhood. Pediatr Neurol 2000;22:361–364.
7 Aydin K, Serdaroglu A, Okuyaz C, Bideci A, Gucuyener K: Serum insulin, leptin, and neuropeptide Y levels in epileptic children treated with valproate. J Child Neurol 2005; 20:848–851.
8 El-Khatib F, Rauchenzauner M, Lechleitner M, Hoppichler F, Naser A, Waldmann M, Trinka E, Unterberger I, Bauer G, Luef GJ: Valproate, weight gain and carbohydrate craving: a gender study. Seizure 2007;16: 226–232.
9 Grosso S, Mostardini R, Piccini B, Balestri P: Body mass index and serum lipid changes during treatment with valproic acid in children with epilepsy. Ann Pharmacother 2009; 43:45–50.
10 Masuccio F, Verrotti A, Chiavaroli V, de Giorgis T, Giannini C, Chiarelli F, Mohn A: Weight gain and insulin resistance in children treated with valproate: the influence of time. J Child Neurol 2010;25:941–947.
11 Kobau R, DiIorio CA, Price PH, Thurman DJ, Martin LM, Ridings DL, Henry TR: Prevalence of epilepsy and health status of adults with epilepsy in Georgia and Tennessee: Behavioral Risk Factor Surveillance System, 2002. Epilepsy Behav 2004;5:358–366.
12 Breum L, Astrup A, Gram L, Andersen T, Stokholm KH, Christensen NJ, Werdelin L, Madsen J: Metabolic changes during treatment with valproate in humans: implication for untoward weight gain. Metabolism 1992; 41:666–670.
13 Brown R, Imran SA, Ur E, Wilkinson M: Valproic acid and CEBPalpha-mediated regulation of adipokine gene expression in hypothalamic neurons and 3T3-L1 adipocytes. Neuroendocrinology 2008;88:25–34.
14 Verrotti A, la Torre R, Trotta D, Mohn A, Chiarelli F: Valproate-induced insulin resistance and obesity in children. Horm Res 2009;71:125–131.
15 Hamed SA, Fida NM, Hamed EA: States of serum leptin and insulin in children with epilepsy: risk predictors of weight gain. Eur J Paediatr Neurol 2009;13:261–268.
16 Lagace DC, McLeod RS, Nachtigal MW: Valproic acid inhibits leptin secretion and reduces leptin messenger ribonucleic acid levels in adipocytes. Endocrinology 2004;145: 5493–5503.
17 Pylvänen V, Pakarine n A, Knip M, Isojärvi J: Characterization of insulin secretion in Valproate-treated patients with epilepsy. Epilepsia 2006;47:1460–1464.
18 Prodam F, Bellone S, Casara G, De Rienzo F, Grassino EC, Bonsignori I, Demarchi I, Rapa A, Radetti G, Bona G: Ghrelin levels are reduced in prepubertal epileptic children under treatment with carbamazepine or valproic acid. Epilepsia 2010;51:312–315.
19 Greco R, Latini G, Chiarelli F, Iannetti P, Verrotti A: Leptin, ghrelin, and adiponectin in epileptic patients treated with valproic acid. Neurology 2005;65:1808–1809.
20 Gungor S, Yücel G, Akinci A, Tabel Y, Ozerol IH, Yologlu S: The role of ghrelin in weight gain and growth in epileptic children using valproate. J Child Neurol 2007;22:1384–1388.
21 Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989;30:389–399.
22 Scheuer ML, Pedley TA: The evaluation and treatment of seizures. N Engl J Med 1990; 323:1468–1474.
23 Marshall WA, Tanner JM: Variations in patterns of pubertal changes in girls. Arch Dis Child 1969;44:291–303.
24 Marshall WA, Tanner JM: Variations in patterns of pubertal changes in boys. Arch Dis Child 1970;45:13–23.
25 Neyzi O, Binyildiz P, Alp H: Growth standards for Turkish children: heights and weights. Courier 1979;29:553–558.
26 Neyzi O, Furman A, Bundak R, Gunoz H, Darendeliler F, Bas F: Growth references for Turkish children aged 6 to 18 years. Acta Paediatr 2006;95:1635–1641.
27 Turan S, Bereket A, Furman A, Omar A, Berber M, Ozen A, Akbenlioglu C, Haklar G: The effect of economic status on height, insulin-like growth factor (IGF)-I and IGF binding protein-3 concentrations in healthy Turkish children. Eur J Clin Nutr 2007;61: 752–758.
28 Bereket A, Turan S, Omar A, Berber M, Ozen A, Akbenlioglu C, Haklar G: Serum IGF-I and IGFBP-3 levels of Turkish children during childhood and adolescence: establishment of reference ranges with emphasis on puberty. Horm Res 2006;65:96–105.

29 Egger J, Brett EM: Effects of sodium valproate in 100 children with special reference to weight. Br Med J (Clin Res Ed) 1981;283:577–581.
30 Hamed SA: Leptin and insulin homeostasis in epilepsy: relation to weight adverse conditions. Epilepsy Res 2007;75:1–9.
31 Cansu A: Antiepileptic drugs and hormones in children. Epilepsy Res 2010;89:89–95.
32 Biton V: Effect of antiepileptic drugs on bodyweight: overview and clinical implications for the treatment of epilepsy. CNS Drugs 2003;17:781–791.
33 Jallon P, Picard F: Bodyweight gain and anticonvulsants: a comparative review. Drug Saf 2001;24:969–978.
34 Biton V, Mirza W, Montouris G, Vuong A, Hammer AE, Barrett PS: Weight change associated with valproate and lamotrigine monotherapy in patients with epilepsy. Neurology 2001;56:172–177.
35 Privitera MD, Brodie MJ, Mattson RH, Chadwick DW, Neto W, Wang S; EPMN 105 Study Group: Topiramate, carbamazepine and valproate monotherapy: double-blind comparison in newly diagnosed epilepsy. Acta Neurol Scand 2003;107:165–175.
36 Espinosa PS, Salazar JC, Yu L, Mendiondo MS, Robertson WC, Baumann RJ: Lack of valproic acid-associated weight gain in prepubertal children. Pediatr Neurol 2008;39:177–180.
37 de Vries L, Karasik A, Landau Z, Phillip M, Kiviti S, Goldberg-Stern H: Endocrine effects of valproate in adolescent girls with epilepsy. Epilepsia 2007;48:470–477.
38 Elmquist JK, Elias CF, Saper CB: From lesions to leptin: hypothalamic control of food intake and body weight. Neuron 1999;22:221–232.
39 Sahu A: Leptin signaling in the hypothalamus: emphasis on energy homeostasis and leptin resistance. Front Neuroendocrinol 2003;24:225–253.
40 Stanley BG, Leibowitz SF: Neuropeptide Y injected in the paraventricular hypothalamus: a powerful stimulant of feeding behavior. Proc Natl Acad Sci USA 1985;82:3940–3943.
41 Gerald C, Walker MW, Criscione L, Gustafson EL, Batzl-Hartmann C, Smith KE, Vaysse P, Durkin MM, Laz TM, Linemeyer DL, Schaffhauser AO, Whitebread S, Hofbauer KG, Taber RI, Branchek TA, Weinshank RL: A receptor subtype involved in neuropeptide-Y-induced food intake. Nature 1996;382:168–171.
42 Duhault J, Boulanger M, Chamorro S, Boutin JA, Della Zuana O, Douillet E, Fauchère JL, Félétou M, Germain M, Husson B, Vega AM, Renard P, Tisserand F: Food intake regulation in rodents: Y5 or Y1 NPY receptors or both? Can J Physiol Pharmacol 2000;78:173–185.
43 Brill J, Lee M, Zhao S, Fernald RD, Huguenard JR: Chronic valproic acid treatment triggers increased neuropeptide Y expression and signaling in rat nucleus reticularis thalami. J Neurosci 2006;26:6813–6822.
44 Wang J, Akabayashi A, Yu H, Dourmashkin J, Alexander JT, Silva I, Lighter J, Leibowitz SF: Hypothalamic galanin: control by signals of fat metabolism. Brain Res 1998;31:7–20.
45 Nagase H, Bray G, York D: Effect of galanin and enterostatin on sympathetic nerve activity to interscapular brown adipose tissue. Brain Res 1996;12:44–50.
46 Shi RF, Wang KL, Li QH, Zheng HC, Yang HF, Tang HX, Sun SZ, Wang LH, Tian J: Changes of body weight and galanin in epileptic children treated with topiramate (in Chinese). Zhonghua Er Ke Za Zhi 2007;45:199–202.
47 Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, Purnell JQ: Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med 2002;346:1623–1630.

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