



# Valproate sodium enhances body weight gain in patients with childhood epilepsy: A pathogenic mechanisms and open-label clinical trial of behavior therapy

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## ABSTRACT

**Objectives:** Excessive weight gain associated with valproate sodium (VPA) may predispose patients with epilepsy to other health problems such as insulin resistance. The purpose of this study was to examine the changes in body weight and several biochemical parameters in children receiving VPA treatment. The effects of behavior therapy for epileptic children with VPA-induced weight gain are discussed.

**Methods:** Fifteen patients newly diagnosed with epilepsy were included in the study. The following parameters were measured: body weight, body mass index (BMI), serum glucose, serum insulin, serum VPA concentration and serum free carnitine. In addition, behavior therapy was introduced at the initiation of VPA therapy, and lasted at least for 2 years.

**Results:** After 6 months of follow-up, there were eight (53%) patients in whom weight gain was demonstrated. Significant increases in the serum insulin level and the insulin/glucose ratio were observed in the weight gain group ( $p < 0.01$ ). All patients with significant weight gain showed increased appetite. However, BMI stopped increasing with intensive behavior therapy.

**Conclusions:** These findings suggest that an increase in serum insulin and insulin/glucose levels may cause weight gain, possibly by stimulating appetite, and that weight changes seem to be reversible with intensive behavior therapy without discontinuation of VPA.

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## 1. Introduction

Valproate sodium (VPA) is a broad-spectrum anticonvulsant. VPA is not a sedative and it is associated with fewer cognitive or behavioral effects than other drugs such as phenobarbital.<sup>1</sup> On the other hand, VPA causes numerous side effects.<sup>2</sup> Patients with chronic epilepsy treated with VPA did not self-report any improvement in health-related quality of life.<sup>3</sup> Moreover, use of VPA in patients with epilepsy is associated with an increase in body weight that can interfere with treatment compliance.

Weight gain is a well-known adverse effect of VPA treatment, occurring in 40% of children.<sup>4</sup> Weight gain is the most common reason for patients to discontinue VPA treatment.<sup>5–7</sup> In a recent study, 38% of VPA-treated patients gained more than 10% of their body weight compared with 8% of patients treated with lamotrigine.<sup>8</sup> Further, weight gain associated with VPA seems to be appetite-related and not metabolic.<sup>9</sup> Although there has been recent interest in weight gain accompanying VPA therapy,

the pathogenic mechanisms of this adverse effect remain unclear. In the study by Isojarvi et al., hyperandrogenism and polycystic ovaries were associated with weight gain, elevated fasting serum insulin levels, and serum low insulin-like growth factor-binding protein 1 (IGFBP-1) levels in women taking VPA for epilepsy.<sup>10</sup> These findings suggest that the weight gain can be progressive and is associated with hyperinsulinemia and low serum IGFBP-1 levels, which may lead to hyperandrogenism and polycystic ovaries. Thus, hyperinsulinemia may cause weight gain in patients taking VPA.

Many adverse health effects generally associated with adult obesity are now being seen in obese adolescents.<sup>11,12</sup> Behavior therapy is a psychological treatment based on the theory that the problem in question is maintained by certain dysfunctional cognitions and beliefs.<sup>13,14</sup> Basic components of behavior therapy are changing a child's eating habits, providing a moderate exercise program, implementing self-regulation skills and providing parental and peer support.<sup>15</sup> Excessive weight (e.g., obesity) is a complex interplay of environmental, social, economic, and behavioral factors, acting on the background of genetic susceptibility. Therefore, weight-control interventions are multifaceted and excessive weight or weight gain not simply treatable with behavior therapy. However, successful weight management may be possible without strict diet prescriptions.<sup>16,17</sup>

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The purpose of this study was to examine the changes in body weight and several biochemical and endocrine parameters in older children and adolescents receiving VPA treatment. In addition, the effect of behavior therapy on VPA-induced weight gain is discussed.

## 2. Patients and methods

Fifteen patients (5 males and 10 females, mean age 11.1 years, range 7–16 years of age) newly diagnosed with epilepsy and for whom VPA was considered the most suitable treatment<sup>18</sup> were included in the study after informed parental consent was obtained. Patients were referred to the University of Yamanashi Hospital and its satellite hospitals between April 1, 2003 and March 31, 2005. Seven patients had idiopathic generalized epilepsy, and eight patients had idiopathic partial epilepsy with secondary generalization. Brain magnetic resonance imaging or computed tomographic scans were interpreted as normal. The average daily dose of VPA was 17.4 mg/kg (range, 13.6–23.1 mg/kg). No patients required other anticonvulsants in addition to VPA.

Participants were included if their weight and height were documented at the initiation of VPA treatment and if they returned for at least one follow-up visit during which their weight and height were re-measured. Those who were followed up for fewer than 3 months or who discontinued VPA treatment within 3 months of initiation, were excluded. Patients were also excluded if they received concurrent medication known to affect weight, such as antipsychotic agents, or stimulants.

The main screening assessments included seizure frequency, vital signs, physical and neurologic examinations, medical history, and standard clinical laboratory tests. Weight and height measurements were recorded at the initiation of VPA therapy and at all scheduled visits. Body mass index (BMI) was calculated at each of these points by dividing the weight in kilograms by the square of the height in meters. National growth chart findings based on data collected in a survey of Japanese children were used to obtain the mean body weight for height. The BMI category was defined as underweight, <18.5, appropriate, 18.5–21.5, potentially overweight, 21.5–25.0 and overweight, >25.0. Patients with a BMI increase exceeding 1.0 per 3 months were categorized in the weight gain group. In addition, we asked participants about appetite using the question “Has your appetite increased or decreased since starting the treatment?”

A blood sample was obtained between 8:30 and 9:00 am after an overnight fast and before breakfast. Weight and height were measured at the same time. The following parameters were measured using commercially available radioimmunoassay kits: serum glucose, serum insulin, serum VPA concentration, serum-free carnitine, triiodothyronine, thyroxine, thyroid-stimulating hormone, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.

Potential predictors of BMI category at follow-up and BMI difference, including age at initiation of VPA, gender, VPA dose per weight (average maintenance dose, highest dose used), and average serum level, were recorded. The assessment was performed every 3 months.

The behavior therapy intervention was carried out by a pediatric neurologist trained in behavior therapy. Oral instruction for avoidance of weight gain was introduced to all patients at the initiation of VPA therapy. Our oral instructions for avoiding weight gain included the evidence that weight gain may cause metabolic and psychological problems. Further, programmed behavior therapy was introduced to the weight-gainers at 6 months after VPA initiation. The intervention was conducted through work with both the children and their parents. The program of behavior therapy was based on lifestyle modification using a simple

checklist.<sup>19</sup> Asayama et al. previously reported that the majority of the boys and nearly half of the girls participating in behavior therapy for longer than 200 days grew out of their obesity.<sup>20</sup> The behavior strategies consisted of several instructions as follows: (1) children and their families were instructed to regularly to eat three meals and one afternoon snack daily, avoiding intake of extra snacks, juices, oily (greasy) food additives, sugar and candies, and to drink no more than 200 ml of milk; (2) reduced caloric intake was not prescribed but patients were advised to observe the recommended daily allowance of food energy for each age and sex set by the Ministry of Education, Science and Culture of Japan; (3) children were instructed to play video or computer games for no more than 1 h a day; and (4) each child (or family) kept a checklist to evaluate (yes or no) whether they observed the seven recommendations (three meals and a snack, no night eating, video game limitations and doing their chores, etc.) on a daily basis. They reported their checklist scores (max. 7 points  $\times$  7 days per week) once every 3 months. We instructed the family on these points repeatedly at each visit (every 3 months). In this treatment program, diet was not restricted and fixed exercise regimes were not prescribed. Therefore, weight gain or excess were essentially intended to be ameliorated by life style modification with a modest change in body weight.<sup>19</sup> There was no other psychoeducational component to the intervention. The duration of behavior therapy was 15 min per session. The sessions were delivered as part of the routine epilepsy visit every 3 months. The behavior therapy was intensified as a result of participant or parental feedback from the checklist. The maximum–minimum frequency and duration of sessions was every 2–3 months and 15–30 min per session, respectively. The behavior therapy intervention lasted for at least two years.

We collected other data every 3 months in addition to the family's report of their adherence to recommendations. We assessed whether patients report their appetite as increased or decreased via the “appetite increased” question from the participants' reports. All data are presented as means for each group measure. The BMI difference for the two groups and the comparison between the two groups of patients was performed using ANOVA and Dunnett's test when appropriate. For statistical analysis, a *p*-value <0.05 was defined as statistically significant.

## 3. Results

We followed all patients from the beginning of therapy for at least two years. In the six months after the first observation, there were eight (53%) patients in whom weight gain was demonstrated (defined as an increase of BMI >1.0 in 3 months). However, no patients remained in the weight gain group at the end of the follow-up. Therefore, we subdivided the patients into two groups according to their BMI halfway through behavior therapy. Behavior therapy lasted for at least two years. Patient data are summarized in Table 1. There were no significant differences in body weight and BMI at VPA initiation between the weight gain (*n* = 8; mean age, 11.9 years; age range, 8–16 years; male:female = 0:8) and no weight gain groups (*n* = 7; mean age, 10.1 years; age range, 7–13 years; male:female = 5:2). However, the difference in BMI became significant during the course of the study (*p* < 0.01). Therefore, this subdivision was appropriate. We observed excellent seizure control with complete disappearance of seizures after 2 months of therapy in all patients in both groups. Thus, the severity and frequency of seizures were similar in the two groups. All patients remained seizure free until the end of the study. No patients required additional anticonvulsant medication during the study.

The mean BMI was 19.1 at initiation of VPA therapy for the entire sample (S.D., 2.4; range, 15.8–22.9). At onset, six (40.0%) subjects were in the underweight range, seven (46.7%) were in the

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