Effect of valproic acid monotherapy on serum leptin and ghrelin levels in epileptic children (literature review)

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Abstract.
The incidence of epilepsy varies between industrialized countries and developing ones. Anti-epileptic drugs are the standard of care for epilepsy management with sodium valproate being the most commonly prescribed anti-epileptic drug in children with epilepsy. Valproic acid (VPA) is a first generation anti-epileptic drug used widely as a monotherapy or part of polytherapy for a variety of seizures in children more than two years of age. It is stated that long-term treatment with VPA is associated with risks such as weight gain, hyperinsulinemia, metabolic syndrome, and cardiovascular disease. However, the exact pathogenesis of weight gain has not been clearly identified pathogenetically. Studying the effect of VPA monotherapy on possible causative factors (leptin and ghrelin levels) of weight gain would help in undertaking appropriate preventive actions alongside VPA therapy. We review the available literature on the research carried out on this subject in the following sections.

Keywords:
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The incidence of epilepsy varies between industrialized countries and developing ones. In Western countries, new cases per year are estimated to be 33.3–82/100,000, [1] in contrast to the maximum incidence of 187/100,000 estimated in developing countries [1,2]. Valproic acid (2-n-propylpentanoic acid) is a 1st generation anti-epileptic drug used widely as a monotherapy or part of polytherapy for a variety of seizures in children more than 2 years of age [3]. Weight gain is a significant side effect of valproic acid, which has not been clearly identified pathogenetically [4].

Valproic acid (VPA) is one of the most widely prescribed anti-epileptic drugs worldwide. It is stated that long-term treatment with VPA is associated with risks such as weight gain, hyperinsulinemia, metabolic syndrome, and cardiovascular disease [5].

In fact, it is known that weight gain is associated with pathologic consequences related to obesity as reproductive disorders, dyslipidaemia, hypertension, insulin resistance, diabetes mellitus and atherosclerosis and its related vascular implications [6].

It is thus important to study the effect of VPA monotherapy on possible causative factors (leptin and ghrelin levels) of weight gain so that appropriate preventive actions can be taken alongside VPA therapy. We review the available literature on the research carried out on this subject in the following sections.

While leptin is a hormone released by adipose tissue that helps in maintenance of normal body weight by providing a feeling of satiety or fullness and thus, regulating hunger, ghrelin is the “hunger hormone” and stimulates food intake.

VPA is a selective inhibitor of histone deacetylase, which plays important roles in epigenetic regulation. While VPA is a widely prescribed drug for the treatment of various neurological and neuropsychiatric disorders, important side effects of VPA are weight gain and metabolic disturbances in patients [7]. A recent study stated that 10–70% of children using VPA may have side effects related to body weight [8]. One study found that 40.4% of patients treated with VPA gained more than 10% of their total body weight, while only 8% of patients treated with other antiepileptics [9]. In another
study, approximately 17% of patients treated with VPA monotherapy have been reported to have obesity [10]. Although the mechanisms of VPA increasing body weight cannot be clearly explained, especially in children; potential mechanisms are associated with increased insulin and leptin levels [11].

The expression of adipokines, that encode neuropeptides such as resistin and leptin, which are involved in the development of insulin resistance and obesity, also increase with VPA therapy [12]. It has been reported that VPA increases leptin, insulin, neuropeptide-y (NPY), and fasting insulin-glucose ratio, while reducing beta-oxidation of lipids due to carnitine deprivation. It is known that due to the lipogenic effect of insulin, it stimulates triacylglycerol and fatty acid synthesis, suppresses fatty acid oxidation, and leptin acts as an antagonist to insulin with its lipolytic effect. However, this balance is important in maintaining weight, it is thought that VPA therapy increases energy balance and appetite by increasing NPY levels and through GABAergic agonistic effect on hypothalamus. Especially in the early stages of VPA therapy, the increase in ghrelin levels activates the neuropeptide Y pathway, which stimulates appetite and food intake [13].

Ghrelin is a lipophilic peptide secreted by specialized enterochromaffin cells lining the gastric fundus mucosa. It is the most recent hormone identified as a regulator of energy balance. It is a major determinant of food intake and satiety [14]. Plasma ghrelin level increases before meals and decreases postprandially [15]. Ghrelin regulates the secretion of leptin and insulin [16]. It stimulates food intake through metabolic effects contradictory to the effects of leptin and increases the consumption of carbohydrates while decreasing fat consumption. Thus, it ensures energy gain and storage [17]. The increased stimulation of eating by ghrelin has been suggested to be mediated in part by the arcuate nucleus and largely associated with neuropeptide Y and agouti-related peptide [18]. It increases the appetite and food intake through such mechanisms and leads to weight gain, in addition to stimulating hyperinsulinemia and dietary obesity [19].

A study by Gungor et al (published in 2007) conducted on
35 epileptic patients aged 3-15 years showed a significant increase in serum ghrelin levels ($P < .01$) and a significant decrease in insulin-like growth factor-1 and insulin-like growth factor binding protein-3 levels ($P < .001$ and $P < .01$, respectively) were detected at month 6 of treatment. Serum leptin levels were not significantly decreased in all patients ($P > .05$) [4].

Ghrelin level decreases due to increased calorie intake in patients with obesity and increases during the fasting state and in patients with anorexia nervosa [20]. In a physiological condition, increased ghrelin level is detected in the early morning, in the absence of obesity [21]. A significant increase in serum ghrelin levels detected in prepubertal children, but not in pubertal children, was noted at month 6 of the valproic acid treatment in Gungor et al’s study [4]. In a previous study [22], it was shown that ghrelin levels decreased with age, and its concentration in healthy prepubertal children was found to be higher than in pubertal children. Although increased ghrelin levels and decreased leptin levels were detected in patients in Gungor’s study [4], there was no significant correlation between leptin and ghrelin levels. Another study revealed that 37.5% of postpubertal epileptic women using valproic acid developed obesity at the end of 2 years. Although ghrelin and adiponectin levels were low, leptin and insulin levels were found to be high in that study [15]. The same study also reported that body mass index was positively correlated with leptin and insulin levels and negatively correlated with ghrelin and adiponectin levels. These results are not consistent with results in Gungor et al’s study [4], but it is suggested that the absence of insulin and leptin resistance and the increase in ghrelin levels may be explained by the lack of obesity in Gungor et al’s patients [4]. Furthermore, in the early period of treatment, valproic acid may activate the neuropeptide Y pathway by increasing ghrelin levels, consequently stimulating appetite and food intake, thereby leading to weight gain [4].

It was also shown that ghrelin infusion increased calorie intake 9% to 40% compared to healthy individuals in the control group [23]. Recently, the role of leptin has been questioned in the pathogenesis of valproic acid-associated
weight gain [24]. Leptin, which is synthesized by the adipose tissue, is a hormone regulating body weight and energy metabolism and activates the signal for satiety [25,26]. Serum leptin levels appeared to decrease during the 6-month follow-up of cases in Gungor et al’s study[4]. It has been reported that the leptin level was high in patients using valproic acid who developed obesity, but its level did not change in those who did not [24]. However, some reports indicate that leptin levels are not different in those who did and did not develop obesity [27]. In Gungor et al’s study, decreased leptin levels were attributed to the lack of obesity. In accordance with the literature, a negative correlation between ghrelin and leptin was noted [4].

In a study by Rehman et al on 90 children (45 cases and 45 controls), serum leptin levels were studied in both the groups and it was found to be elevated significantly in VPA group (7.9 ng/ml) than controls (1.6 ng/ml) [11].

A study by Huseyin Kilic et al, carried out on thirty epileptic children treated with VPA, and 20 age-sex-matched healthy children, showed that Leptin levels were significantly higher in the patient group ($P = 0.009$) whereas body mass index values were comparable. There was a positive correlation between leptin and body mass index among both patient ($r = 0.464$, $P = 0.01$) and control groups ($r = 0.734$, $P = 0.0001$). This study demonstrated higher leptin levels in the patient group despite similar BMI values. Hence, it seems likely that VPA causes leptin resistance [28].

In a Turkish study on 30 children and adolescents on VPA monotherapy, 12 month VPA therapy caused weight gain in epileptic children. The BMI-SDSs of the patients increased (1.39±0.56) after VPA treatment (0.94±0.46) ($p<0.05$) [29].

In a study conducted with 35 children aged 3-15 years, body weight, BMI percentiles of the participants increased significantly at the end of the 6th month compared to baseline [4]. In a study of 60 prepubertal children with a mean age of 5.60±1.95 years who received VPA therapy for at least one year, BMI and BMI for age standard deviations were found to be higher in children who received VPA ($p<0.05$) [30]. Wirrell conducted a study in adolescents receiving VPA therapy for a minimum of 2 months and mild-to-moderate weight gain was observed in 58% of the 43 subjects treated with VPA [31].
CONCLUSION

We conclude that while weight gain with valproic acid is the established finding in the reviewed studies, more long term research is required to ascertain the effects of valproic acid on serum leptin and ghrelin levels.

References:


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