ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 06, Issue, 01, pp. 6425-6432, January, 2016

International Journal of
DEVELOPMENT RESEARCH

Full Length Research Article

PRENATAL EXPOSURE TO VALPROIC ACID AND GABAPENTIN ON MATERNAL, FETAL, NEONATAL WEIGHT GAIN AND POSTNATAL DEVELOPMENT

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ARTICLE INFO

Article History:
Received 18th October, 2015
Received in revised form
22nd November, 2015
Accepted 12th December, 2015
Published online 31st January, 2016

Key Words:
Antiepileptics,
Valproic Acid,
GBP,
Body Weight,
Prenatal, Rats.

ABSTRACT

Weight gain in adult patients with hyperphagia is the main concern of long term antiepileptic therapy, but little concern has been taken in pregnant women and their fetal development (weight) as well as long- lasting impact on postnatal growth of the offspring.Sperm positive female C.F. rats were exposed to different doses of Valproic acid (VPA) (50,100 and 200mg/kg body weight) and Gabapentin (GBP) (300 and 400 mg/kg) from gestation day (GD) 0-20 orally with control subjects.Maternal food intake and body weight gain were recorded daily. Half of the pregnant rats of each group were sacrificed on GD21, and fetal body weight was recorded. Remaining dams were allowed to deliver naturally, and their pups were reared up to postnatal day (PND) 56. The offspring's body weights were also determined weekly up to 8 weeks of age. Gestational exposure to VPA and GBP induced dose- dependent substantial reduction of maternal food intake, body weight deficit, fetal weight loss, and long- lasting negative impact on postnatal development and growth of rat offspring at birth and continued till PND 56. This study concludes that short exposure to equivalent therapeutic doses of VPA and GBP to pregnant dams induced not only reduced maternal food consumption and body weight loss but also impaired the fetal growth at full term, and postnatal growth of rat offspring was also found substantially reduced up to 8 weeks of age. Hence, precautions are required before therapeutic use of atypical AEDs like GBP during pregnancy.

INTRODUCTION

For clinical management of epilepsy, both traditional and new generation 'atypical' antiepileptic drugs (AEDs) are available in the world market. Among the classical and newer AEDs, sodiam valproate (VPA) and gabapentin (GBP) are still in use as first- line drug therapy by the physicians against epileptic seizures even during child bearing age group (Dhanawat and Shrivastava, 2012). The atypical AEDs were launched in the global market with better efficacy, tolerability and minimum adverse effects than classical AEDs; and may be recommended even during pregnancy after weighing the benefits and risks to mother and fetus respectively (Finnel, 2010). VPA is commonly used for treatment of generalized seizures and bipolar disorders. The mechanism of action of VPA is through GABAergic system by enhancement of GABA mediated inhibition and blockage of calcium and sodium channels at synapse (Kaindla *et al.,* 2006; Ochoa, 2013).

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GBP is relatively new agent of atypical class of AEDs and widely used for treatment of partial seizures and bipolar disorders (*Xu et al.,* 2003) including neuropathic and post-operative inflammatory pain (Backonja and Glanzman, 2003, Compton *et al.,* 2010). The general mechanism of action of VPA and GBP is similar to other GABA mediated drugs (topiramate, lamotrigine) which interact with GABA A receptors; and facilitates the passage of chloride ions into neuronal cells (Brent, 1982). Kwan *et al.,* (2001) **(**Kwan, *et al.,* 2001**)** reported that GBP may facilitate GABA synthesis and release in the GABAergic neurons. Both GBP and VPA act on GABAergic system. The safety of these AEDs during pregnancy and lactation is a major concern (Pennell, 2005). Among common side effects of frequently used AEDs like VPA and GBP, drug- induced body weight gain is a serious side effect leading to obesity. Anorexia may also be another related adverse effect associated to food consumption. The atypical AEDs generally cause less weight gain than classical AEDs, and some even promote weight loss (Ovsiew, 2004; Marken and Pies, 2006). Literature indicate that weight gain in epileptic patients has been recognized as a common adverse effect of VPA therapy if continued more than three months

and women seem to be more susceptible than men (Martin *et al.,* 2009), Apovian, 2005, Suh *et al.,* 2011). Reports on weight gain and food consumption in animal models are contradictory to clinical studies examined so far. Experimental trials indicate that food intake and body weight gain was found decreased when VPA was administered for short or longer period at equivalent therapeutic doses or subsequent higher doses (Okada *et al.,* 2006; Okada *et al.,* 2009). The mechanism through which VPA induces appropriate weight gain or loss is still controversial (Suh *et al.,* 2011).The current body of growing clinical literature revealed that GBP can cause weight gain in small percentage of patients after prolonged exposure to six months or more (*Xu et al.,* 2003) at higher doses (De Toledo *et al.,*1997; Ness-Abram of, Apovian, 2005). In these clinical trials reports on weight gain are inconsistent. Some investigators reported that some patients had weight gain or no change in weight gain and some patients lost their body weight (De Toledo *et al.,* 1997). Other AEDs can also cause partial weight gain such as carbamazepine (CBZ) (Marken, 2006)) and pregabalin (PGB) (Hamandi and Sander, 2006) while lamotrigine (LTG) was reported as weight neutral (Calabrese *et al.,* 2000) and topiramate (TPM) and zonasamide (ZSM) may induce weight loss in humans (Montouris and Ritter, 1999, Ness-Abramof,Apovian, 2005). Similar to these reports, variation in weight gain was also found in animal models when GBP was administered at higher doses (Petrere and Anderson, 1994; Xu *et al., 2003*). Mechanistically, the basis for drug induced weight modulation in adult human population and animals have not been well established so far. Reports on pregnant subjects are scanty and inconclusive.

Reports on low fetal weight caused by prenatal exposure to GBP, both in clinical (Montouris, 2003.) and experimental investigations (Bittigau *et al.,* 2002**;** Prabhu *et al.,* 2007) are limited.

There is paucity of data on maternal exposure to VPA or GBP, and their long- lasting impact on postnatal developmental and growth of offspring's body weight. The post marketing surveillance of these drugs by pharmaceutical companies and retrospective studies of multinational drugs registry are insufficient to draw any definite conclusion. Most of these studies had limitations and lack of complete information in case of VPA and GBP. Keeping in view of these facts and non-availability of well controlled systematic studies as well as contradictory information on maternal food intake, body weight gain, fetal weight as well as postnatal development and growth of offspring, the present study has been planned to investigate and compare the effect of prenatal exposure to VPA and GBP on maternal, fetal, neonatal and postnatal weight modulation in rats.

MATERIALS AND METHODS

Inbred Charles-Foster rats (150±10g) were maintained under standard laboratory conditions (24±2ºC room temperature, 60 ± 10 relative humidity and 12h light (06.00 to 18.00h)/12h dark cycle (18.00 to 06.00h). Animals were used in accordance to animal welfare act and protocol for use of experimental rats was approved by Institutional Animal Ethics Committee.

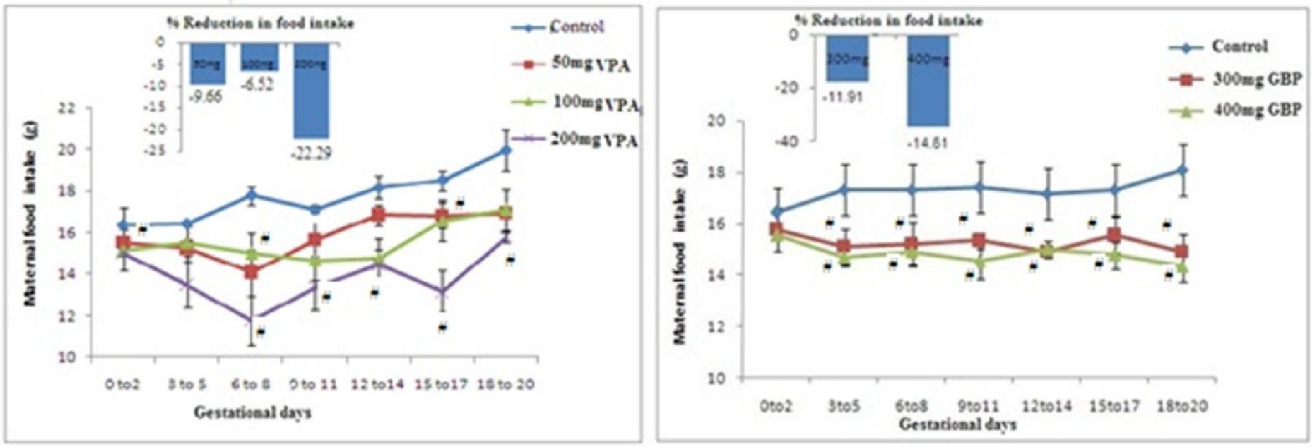

Fig.1. Effect of VPA (50,100 and 200mg) and GBP (300 and 400mg) on maternal food intake at gestational days (GD 0-20). Average of 3 Gestational days were taken to calculate maternal food intake. All data represent Mean ± S.E. value (n=6 per group). # indicate level of significance (p<0.001) between control and exposed groups for two way ANOVA followed by Tukey's multiple comparison test

Literature also indicates that AEDs therapy during pregnancy may induce reduction in intrauterine growth, birth weight, preterm delivery, and head circumference (Verrotti *et al.,* 2011).Several multicenter studies, both prospective and retrospective, revealed that children *in utero* exposed to classical AEDs including VPA were born with reduced body weight (<2.5kg) (Lakshmi and Sunanda, 2008, Molgaard-Nielsen and Hviid , 2011; Verrotti *et al.,* 2011). Reports on low birth weight in experimental animals were also elucidated when VPA was administered during different gestation periods (Finnell *et al.,* 2002; Gupta and Singh, 2007; Okada *et al.,* 2009).

University of Allahabad, Allahabad, India. All animals were housed in transparent polypropylene cages (39×24×15cm) and dry rice bran was used as bedding material. Bedding was changed twice a week to avoid any unhygienic condition. The food pallets and fresh tap water were provided *ad libitum* throughout the experiment. The adult male (10-12 weeks old) and nulliparous female rats (9-10 weeks old) were caged together (1:2 ratio) overnight for mating. On next day (at 08.00h), mating was inferred by the presence of sperms in the vaginal swab, and designated as gestation day zero (GD 0). The sperm positive dams were housed individually in the same sized cages.

All sperms positive female dams (n=42) were randomly separated into two groups; Group-A (VPA exposed, n=18) and Group-B (GBP exposed, n=12); and corresponding controls of each group (n=6/group) were also maintained. Each group was further divided into sub- groups of each drug VPA (50,100 and 200 mg/kg) and GBP (300 and 400 mg/kg) respectively. Both drugs, VPA (trade name Encorate, Sun Pharmaceutical, India) and GBP (trade name Gabapin, Intas Pharmaceutical, India) were purchased from local therapeutic market.

The doses were calculated on the basis of per kg body weight per day to mimic with human therapeutic doses range of VPA (900-2600 mg/day) and GBP (900-3600 mg/day) (Reagan-shaw *et al.,* 2007).The rationale for selection of three and two doses of VPA and GBP respectively were in accordance with maximum human recommended doses (MHRD, for VPA 2600 and GBP 3600mg/kg/day); and considering the higher metabolic rate of rats, 4-6 times faster than humans (Kapur et *al.,* 2003).Therefore, 300mg/kg (5x MHRD), 400 mg/kg (7x MHRD) doses of GBP were selected on the basis of mg/kg bodyweight per day to mimic with therapeutic dose range (Reagan-shaw *et al.,* 2007).

These selected doses were 4-6 times higher to maximum human recommended doses (MHRD), considering the higher metabolic rate of rodents (Kapur et *al.,* 2003) Selected doses of VPA and GBP were prepared freshly with saline on each day and administered (gastric intubation) once daily at 09:00 hr to sperm positive dams with the help of cannula from gestation day 0-20 (GD 0-20). Equal amount of vehicle (saline water) of each drug was also administered to control pregnant dams by same route and time. Twenty-four hours food intake and body weight gain by individual pregnant dams were recorded daily at 09.00 hr till end of the experiment. At GD20 half of the pregnant dams of all the groups were sacrificed after anesthetization with pentobarbitone on GD 20 at 0:900 h, and their near term fetuses were collected by uterectomy and weighed and half of the both control and experimental dams were allowed to deliver naturally. Data on daily food intake and body weight of dams were averaged for three conclusive days for graphical representation.

At birth, all the litters were weighed individually and culled (n= 8 pups per litter), and reared with their biological mothers up to weaning, postnatal day 21 (PND 21). After weaning, male and female pups of each sub-group were segregated in separate cages (n=4/cage) and reared up to PND 56. The offspring of each group were weighed at birth and then once a week till age of PND 56.

Statistical analysis

Data are represented as mean and standard error (Mean ±S.E.). The variables like total food intake and body weight gain by dams and fetal body weight were analyzed using one way analysis of variance (ANOVA) where as maternal food intake, maternal body weight gain and postnatal development (as body weight of offspring) were analyzed using two way ANOVA between time and doses followed by Tukey's multiple comparison test to determine differences amongst groups. For all statistical values alpha level was set as $p<0.05$.

RESULTS AND DISCUSSION

Effect of prenatal exposure to VPA and GBP on maternal food consumption

Two way ANOVA followed by Tukey's multiple comparison test showed significant dose-dependent reduction of food consumption in VPA ($F(3, 18) = 5.98$, $p<0.01$) and GBP ($F(2, 12) = 55.38$, $p<0.001$) treated groups as compared to corresponding control groups. The food intake deficit was also found in dose- response manner in both the drugs, VPA (6.52% and 22.29% at 100 and 200 mg/kg respectively) and GBP (11.91% and 14.61% at 300 and 400 mg/kg respectively) in comparison to respective controls (Fig.1). One way ANOVA followed by Tukey's multiple comparison test also showed substantial reduction of total food intake in VPA ($F(3, 20) = 769$, $p<0.001$) and GBP ($F(2, 15) = 58.35$, $p<0.001$) exposed groups when compared to control groups (Fig.2). The drug induced anorexia/ hypophagia was increased ($p<0.001$) at higher doses of VPA and GBP exposed groups than lower doses.

Effect of prenatal exposure to VPA and GBP on maternal body weight reduction

Two way ANOVA followed by Tukey's multiple comparison test exhibited significant dose-dependent weight reduction in VPA ($F(3, 18) = 14.04$, $p<0.001$) and GBP ($F(2, 12) = 67.61$, $p<0.001$) administered groups in comparison to respective vehicle exposed groups (Fig.3). Maternal body weight was also found to be severely reduced in dose- response fashion in these drugs, VPA (15.23%, 17.16% and 38.73% at 50 mg, 100 and 200 mg/kg respectively) and GBP (17.87% and 34.55% at300 and 400 mg/kg respectively) as compared to corresponding controls. The reduced growth pattern of body weight was clearly discernible at 200 mg VPA and 400 mg GBP treated subjects (Fig.3). One way ANOVA followed by Tukey's multiple comparison test also expressed dose-dependent significant deficit in total body weight gain in VPA ($F(3, 20) = 374.19$, $p<0.001$) and GBP ($F(2, 15) = 637$, $p<0.001$) exposed groups during exposure period when compared to vehicle treated groups (Fig. 4). From these experiments, it does appear that higher doses of VPA (200 mg) and GBP (400 mg) were more inductive to pregnant dams than other doses for maternal food intake in general and body weight gain in particular.

Effect of gestational administration to VPA and GBP on fetal body weight

One way ANOVA followed by Tukey's multiple comparison test displayed significant reduction in fetal body weight in VPA ($F(3, 44) = 640.09$, $p<0.001$) and GBP ($F(2, 33) = 311.33$, $p<0.001$) exposed groups at selected doses in comparison to respective vehicle treated groups (Fig.5). The percentage reduction in fetal body weight was also found in dose-dependent manner in VPA (4.35%, 14.58% and 50.37% at 50, 100 and 200 mg/kg doses respectively) and GBP (20.43% and 28.43 % at 300 and 400 mg doses) treated groups in comparison to corresponding control groups. Hence, a clear dose-response relationship was observed in VPA and GBP treated groups.

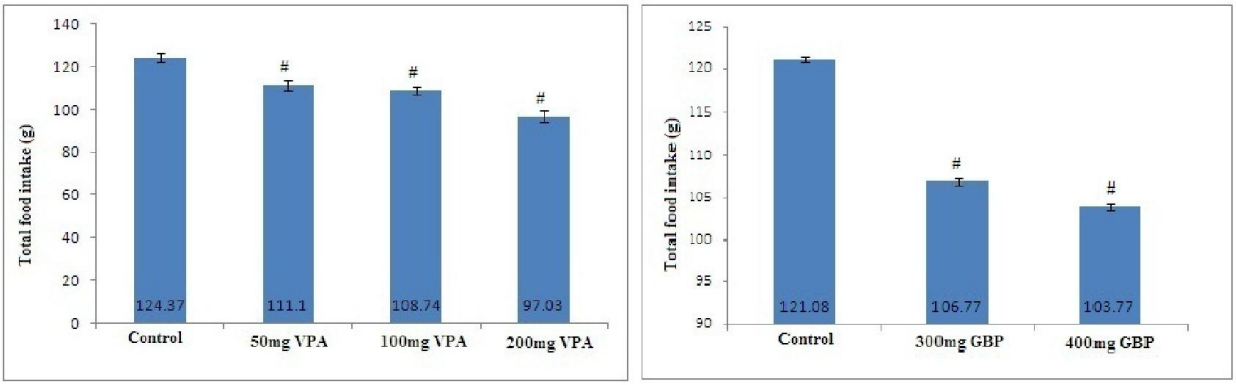

Fig. 2. Effect of VPA (50,100 and 200mg) and GBP (300 and 400mg) on maternal total food intake at gestational days (GD 0-20). All data represent Mean ± S.E. value (n=6 per group). # indicate level of significance (p<0.001) between control and exposed groups for two way ANOVA followed by Tukey's multiple comparison test

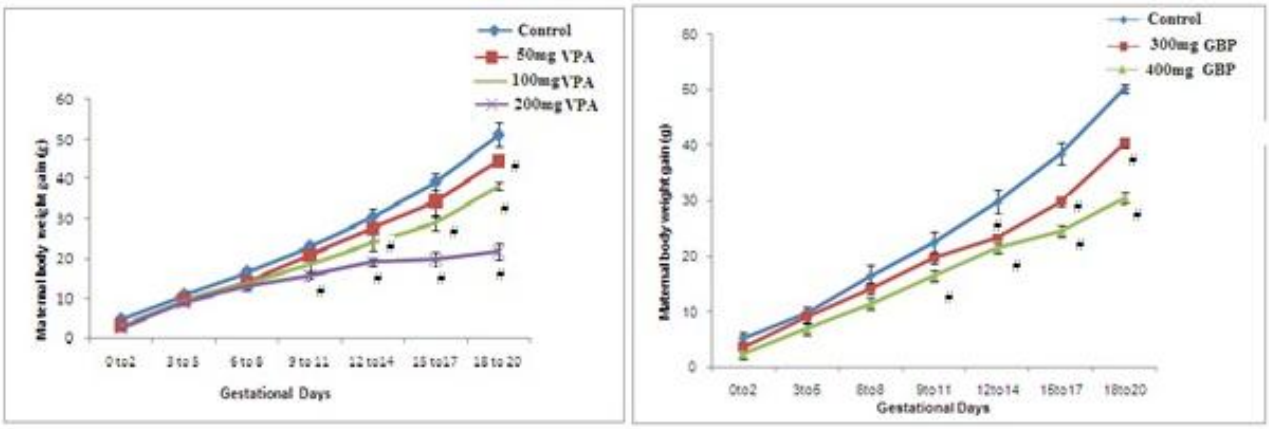

Fig. 3. Effect of VPA (50,100 and 200mg) and GBP (300 and 400mg) on maternal weight gain at gestational days (GD 0-20). All data represent Mean ± S.E. value (n=6 per group). # indicate level of significance (p<0.001) between control and exposed groups for two way ANOVA followed by Tukey's multiple comparison test

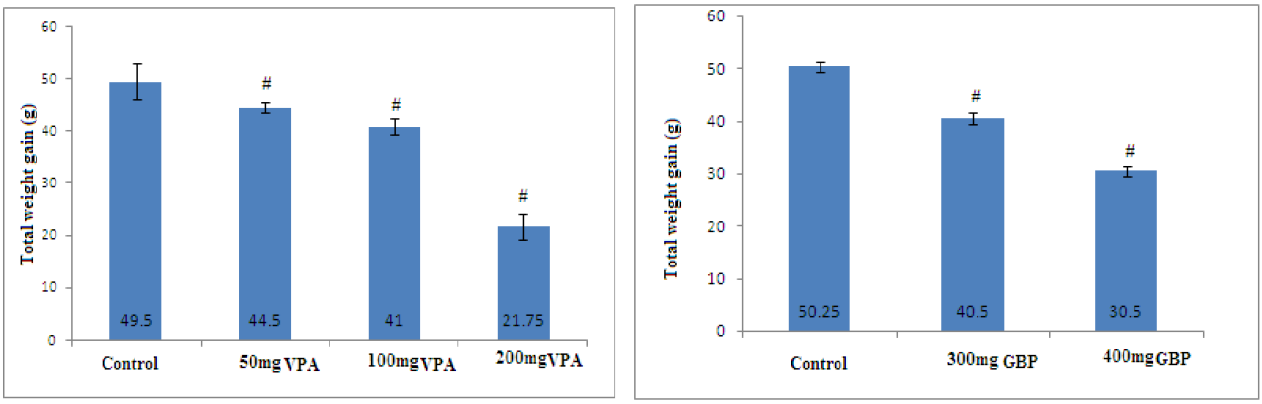

Fig. 4. Effect of VPA (50,100 and 200mg) and GBP (300 and 400mg) on maternal total body weight gain at gestational days (GD 0-20). All data represent Mean ± S.E. value (n=6 per group). # indicate level of significance (p<0.001) between control and exposed groups for two way ANOVA followed by Tukey's multiple comparison test

Effect of gestational exposure to VPA and GBP on post natal development and growth in offspring

None of the animal was died among the prenatally drug treated offspring of all groups till PND 56. Both control and drug treated dams did not show any overt behavioral disturbances during the exposure period. Any unusual behavior/sign in exposed offspring could not be observed during rearing (pre- and post weaning) period.

Two way ANOVA followed by Tukey's multiple comparison test expressed highly significant dose-dependent reduction in offspring's body weight in prenatally VPA ($F(3, 24) = 67.8$, ($p<0.001$)) and GBP ($F(2,16) = 289$, $p<0.001$) exposed groups at selected equivalent therapeutic doses, as compared to unexposed control groups (Fig.5). The average percentage reduction of weekly body weight gain was also found dose-dependent in *in utero* VPA (7.3%, 11.53% and 32.03% respectively) and GBP (32.26% and 40.83% respectively)

treated offspring from PND 1-56 when compared to weekly growth rate of vehicle exposed offspring. The substantial deficit in pups' body weight at birth was continued from weeks 1 to 8 (Fig.5). The VPA and GBP treated offspring could not maintain their 'catch-up growth' rate till eight weeks of age in comparison to vehicle exposed offspring.

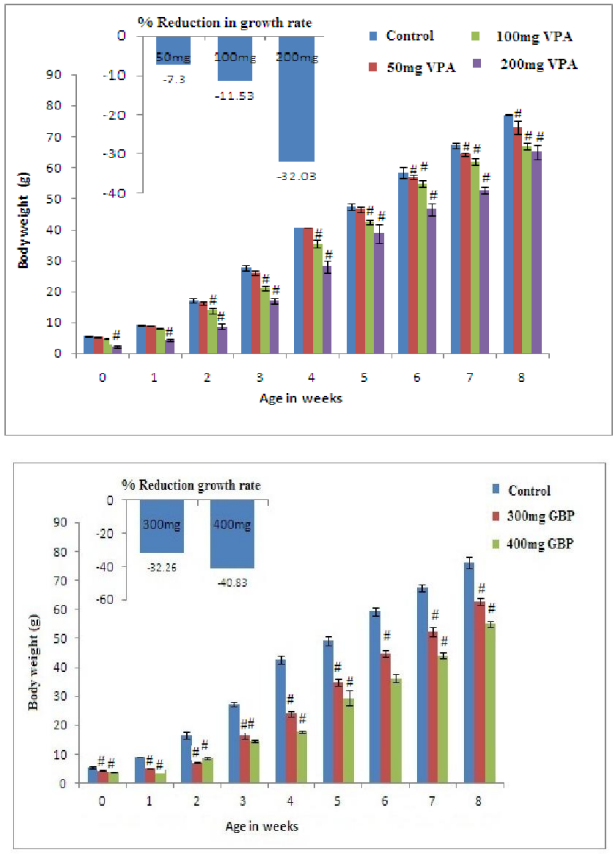

Fig. 5. Effect of VPA (50,100 and 200mg) and GBP (300 and 400mg) on fetal growth rate from PND 1-56 and percentage of reduction in growth rate. All data represent Mean ± S.E. value. (n=6 per group) # indicate level of significance (p<0.001) between control and exposed groups for two way ANOVA followed by Tukey's multiple comparison test

DISCUSSION

The present study revealed that in utero exposure to VPA and GBP induced dose-dependent substantial deficit of maternal food intake and body weight at selected doses. Our results correspond with previous studies reported significant reduction in body weight of pregnant rats/mice exposed to VPA from GD 6-15 at 50 mg and 600 mg doses (Okada *et al.,* (2006) and long-term exposure to GBP at higher doses, 1000 and 2000 mg/kg in rats induced significant suppression of body weight in rats (Reagan-shaw *et al.,* 2007). Animal studies have also not shown weight loss as a consistent effect of GBP.

Petrere and Anderson (1994) (Reagan-shaw *et al.,* 2007) reported no adverse effect on maternal body weight and food consumption when pregnant mice and rats were treated with 500-3000 mg/kg and 60 – 1500 mg/kg dose of GBP from GD 0- 18 respectively, while pregnant rabbits showed reduced food consumption and body weight loss at 1500 mg/kg. In animal studies, no consistent reports are available on body weight gain or loss, but it does appear that higher doses (> 1000 mg/kg) may induce suppression of body weight gain. The present study suggests that even lower doses (300 or 400 mg/kg) of GBP may reduce maternal body weight gain even during short exposure (20 days) in rats. The exact mechanism to induce suppression in maternal body weight gain in rodents is not clearly understood so far. Reports on clinical studies are also variable for weight gain. The newer AEDs generally cause less weight gain than older agents and some even promote weight loss (Hamandi and Sander, 2006) AEDs that promote weight gain include VPA, CBZ and GBP (Morris, 1995).

While TPM and ZSM may induce weight loss, but LTG is weight–neutral in patients (Ness-Abramof,Apovian, 2005). De Toledo *et al*., (1997) (De Toledo *et al.,* 1997) reported that about 57 % patients had weight gain and 36 % had no change and 7 % had reduced body weight gain when GBP was exposed above the 3000 mg/day for one year. Previous studies have also reported the weight gain in patients receiving 900-2400 mg/day of GBP (Wallace, 2001). It seems that GBP may cause weight gain in small portion of patients. The weight gain appears to be more common with higher doses (> 3000 mg/day) and long term therapy (> 6 months). Our healths are not in consonant with clinical studies where majority of patients were associated with weight gain during drug therapy. Among several clinical side effects, maternal catalepsy or anorexia is one of the most occurring effects of anticonvulsant therapy. It is more prevalent with typical AEDs than atypical agents. In clinical studies, it is difficult to interpret the possible mechanisms of maternal body weight gain in presence of anorexia in patients who are associated to AEDs therapy.

In such cases, anorexia induced mild under nutrition may not be responsible for maternal weight gain or loss. In our study, both drugs, VPA and GBP induced substantial deficit in maternal body weight and food intake. Hence, drug induced anorexia may be one of the causative agent. But, it was also concluded that maternal food intake was reduced up to 14.61 % in GBP and 22.29 % in VPA treatment while maternal body weight deficit was 34.55 % in GBP and 38.73 % in VPA exposed subjects at higher doses respectively. At lower doses of VPA or GBP, reduction in food intake was 6-9 % in VPA and about 12 % in GBP while maternal body weight deficit was 15-17 % in VPA and about 18 % in GBP treatment group respectively. It is elucidated from these data that any deficit in maternal food intake may induce about 1 to > 2 times higher impact on maternal body weight loss; hence, GBP may not be comparatively safe than VPA. It may also be revealed that drug induced anorexia may not be a solo reason for reduction in maternal body weight in drug treated groups.

The involvement of other mechanisms, possibly metabolic dys-regulation, hyperactivity with increased energy expenditure, endocrine/hormonal alteration especially prolactin (new) for inducing substantial body weight deficit in AEDs exposed mothers may not be ruled out. It is well documented that lateral hypothalamus is an area of brain known to play an integral part in the control of food intake. Some workers have also reported the involvement of orexin, a neuropeptide synthesized from hypothalamus, in regulation of

feeding behavior, sleep/wake cycle and spontaneous physical activity (Wilton and Shakir, 2002). Baptista *et al.,* (2001, 2004) (Baptista *et al.,* 2001; Baptista *et al.,* 2004) elucidated that leptin, another neuropeptide released by hypothalamus, reduces food intake and increases energy expenditure thus reduces body weight by affecting the feeding pattern (Panariello *et al.,* 2011). Both leptin and neuropeptide-Y are neuromodulators important to feeding and body weight regulation. A well studied mechanism by which prolactin may increase body weight is related to a feedback loop involving the eating-stimulatory peptide galanin, which is synthesized in the para-ventricular hypothalamus and stimulates prolactin production. It was also reported that some molecules of these agents are extremely sensitive for suppression of food intake as direct affect on appetite through hypothalamic neuron (Oh-I *et al.,* 2006). It is speculated that these drugs could not enhanced prolactin level due to short exposure of drugs; hence excessive body weight gain was not discernible. Therefore, possibility of involvement of multifactorial mechanisms may not be clear.

This study further demonstrates that both drugs, VPA and GBP caused substantial dose-dependent fetal growth retardation (body weight). The percentage reduction in fetal body weight was more severe (63.92%) at higher dose of VPA (200 mg) than GBP (26.29%) at 400 mg, while it was found similar at intermediate doses of VPA and GBP. It does appear that GBP is less fetotoxic than VPA. These data corroborate well with other investigators who have reported as reduced birth weight of offspring or fetal growth retardation whose mothers have been exposed to selected doses of VPA in animal models (Finnell *et al.,* 2002; Ong *et al.,* 1983). Ong *et al.,* (1983) has reported reduced fetal body weight at higher dose of VPA (600 mg/kg) exposed to pregnant rats from GD 6-15, while no such deficit of fetal body weight was noticed at 50 and 150 mg of VPA. Experimental studies on GBP induced fetal growth retardation are less in number for valid comparisons.

In the recent past, Prakesh *et al.,* (2008) elucidated reduction in body weight of live fetuses with stunting in size at different doses of GBP (113, 226 and 452 mg/kg) at different gestation periods. In rodents, GBP has been shown to be growth stunted when pregnant dams were received oral dose, approximately 1-5 times the MHRD during organogenesis (Neurontin, 1998). In one study, GBP was found to be fetotoxic at higher doses in rodent (McLean, 1995) Clinical literature on maternal exposure to GBP and its effect on IUGR are limited (Montouris, 2003). However, the involvement of other possible mechanisms for inducing fetal growth restriction, like involvement of estrogen biosynthesis, leptin expression, placental dysfunction (Raha *et al.,* 2012) increased oxidative stress and poor antioxidant mechanism (Sigler *et al.,* 1995) poor mitochondrial function (Liu *et al.,* 2012) and enhanced apoptosis (Bittigau *et al.,* 2002) may not be ignored.

It is well established from the literature that prenatally undernourished offspring usually display fast 'catch- up growth' in due course of postnatal development (Gilbert *et al.,* 2010).Thus, moderate under nutrition during development (<50% restriction of diet) may lead to equal postnatal growth at least at PND 7 and non-significant reduction up to PND 22 and in adult stage (Gilbert *et al.,* 2010).In the present study, those offspring who were prenatally exposed to VPA or GBP couldn't maintain their postnatal development and growth till 8 weeks of age with control offspring of the same age group. Though catch-up growth of the offspring was reflected in dose-dependent manner but it was unlike the undernourished condition. Hence, on the basis of these arguments it may be concluded that maternal body weight was significantly reduced mainly due to drug induced effects, directly or indirectly, in spite of anorexia or maternal catalepsy. The exact mechanism of action for inducing maternal body weight deficit in AEDs exposed rats is still not clearly defined. Hence, it is presumed that multi-factorial mechanisms might be involved which needs further investigations on this issue.

Conclusion

Our study concludes that *in utero* exposure to VPA or GBP at different selected doses not only induced maternal adverse effects as substantial deficit in food consumption and body weight loss but also induced fetal toxicity as significantly fetal weight restriction like IUGR; and expressed long-lasting impact on postnatal growth of young –adult rat offspring. Therefore, caution must be taken before prescribing the newer AEDs like GBP even during short gestation period considering the window of susceptibility during fetal development.

Acknowledgement

Authors are thankful to Head, Department of Zoology, University of Allahabad, Allahabad for providing laboratory facilities. This research work was financially supported by University of Allahabad. Prof. Mandavi Singh, IMS, BHU is thankfully acknowledged for her critical suggestions and valid discussion.

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