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Research Article

NEUROARCHITECTURAL DISTURBANCES IN FETAL HIPPOCAMPUS AND NEUROFUNCTIONAL IMPAIRMENT IN YOUNG RATS PRENATALLY EXPOSED TO ANTIEPILEPTIC GABAPENTIN

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ABSTRACT

Antiepileptic drugs are used to treat seizures in pregnant women may cause cognitive impairment in children. It is still unknown whether *in utero* exposure to gabapentin (GBP) may induce neuropathological changes in fetal brain, and related functional disturbances in adolescents. Therefore, present study has been designed to evaluate the effects of prenatal exposure to GBP on neurostructural changes in fetal hippocampus; and their long-lasting impact on cognitive performance in young rat offspring; and to compare these findings with a classical drug, valproic acid (VPA) for drug safety concern. The nulliparous pregnant rats were exposed to GBP (300 and 400mg) and VPA (50,100 and 200mg) from gestation day (GD) 0-20. On GD 21, about half of the pregnant rats of all groups were sacrificed; their fetal brains were processed for paraffin microtomy of hippocampal area. Remaining drug treated and control dams were allowed to deliver naturally, and pups were reared with their biological mothers up to postnatal day (PND) 21. At 8 weeks of age, offspring were subjected to test of cognition (T- maze). Neurohistopathological evaluation of GBP and VPA exposed fetal brains revealed that laminar architecture of typical three layered hippocampal cortex was found to be less developed, poorly differentiated and substantially reduced in size in comparison to vehicle treated group. Further, prenatally drug treated young offspring displayed cognitive impairment performance in T maze. These findings suggest that prenatal exposure to GBP or VPA during organogenesis showed not only neuroarchitectural alterations but also induced long-lasting impact on cognitive performance in young offspring.

INTRODUCTION

WHO (2001) estimated that about 50 million people (1–2% of human population) in the world are suffering with various forms of epilepsy, and nearly 80% of the people who have epilepsy live in developing countries. About one third of the global epileptic population belong to women of reproductive age group [Begum and Thomas, 2013]. For therapeutic treatment of epilepsy in adult population of both gender, classical or traditional (Ist generation) and newer or atypical (2nd generation) antiepileptic drugs (AEDs) are available, and about 80% cases are successfully treated, but there is still treatment gap because both seizures and AEDs treatment during pregnancy are thought to have negatively influence on the child development (Harden *et al*., 2009). Hence, physicians always have dilemma to treat pregnant women with epilepsy, since classical AEDs are associated to congenital birth defects, developmental neurotoxicity, developmental delay and neurobehavioural alterations in offspring, whereas these potential effects of newer AEDs have not been well established in clinical and preclinical studies (Kimford and Loring, 2016; Veiby *et al*., 2014). Although 2nd generation AEDs like oxcarbamazepine (OCBZ), gabapentin (GBP), topiramate and lamotrigine (LTG) etc. have better efficacy, pharmacodynamics, pharmacokinetics and minimal side effects in comparison to Ist generation AEDs viz. phenobarbital (PHB), carbamazepine (CBZ), valproate (VPA), phenytoin (PHT) etc. (Tomson and Battino, 2008; Hill, *et al*., 2010), but sporadic incidences of congenital anomalies, neuronal injuries in fetal brain and neurobehavioural disturbances in young offspring were reported in experimental and clinical investigations.

The long-term effects into adulthood induced by in utero exposure to newer AEDs have not been extensively studied, even though there are some follow-up studies indicating that almost all AEDs have negative effects on neurobehaviour including cognition (Kimford *et. al*., 2016; Eddy, *et al*., 2011). Thus, limited information is available on prenatal exposure to GBP on neurostructural changes in hippocampus of fetal brain and their long-lasting impact on neurobehavioural changes in rodent offspring (Wlodarczyk *et. al*. 2012).

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Therefore, present study was undertaken to elucidate the effects of in utero exposure to GBP, during vulnerable period of brain development, on developmental neurotoxic potential (neuroarchitectural pattern) in fetal hippocampus, and its long-lasting impact on cognitive impairment in young rat offspring; and to compare these effects with VPA, a classical AED well known for its teratogenic and developmental neurotoxic potential. In this study, VPA was used as a positive control whereas saline (vehicle) was used as a negative control, as mentioned by Frankel *et al*. (2016).

MATERIAL AND METHODS

Animals

Inbred Charles-Foster rats (150 ± 10 g) were acclimatized before experimentation. These rats were maintained under standard laboratory conditions (24 ± 2^0 C room temperature, 60 ± 10 relative humidity and 12 h light (06.00–18.00 h)/12 h dark cycle (06.00–18.00 h). Animals were maintained and used in accordance with the Animal Welfare Act and the protocol for use of experimental rats was approved by Institutional Animal Ethics Committee.

Experimental design, drug exposure and rationale for dose selection

All positive female rats (n=28) were randomly separated into six groups: Group A (n=8, vehicle exposed/ control), Group B (n=4, 300mg/kg GBP), Group C (n=4, 400mg/kg GBP), Group D (n=4, 50mg/kg VPA), Group E ((n=4, 100mg/kg VPA) and Group F (n=4, 200mg/kg VPA) respectively. Freshly prepared selected doses of the drugs (VPA and GBP) were administered to experimental pregnant rats through gavage with the help of cannula at 09.00 hrs from GD 0-20. The control dams were treated with equal dose of vehicle (water) through same route and time. The rationale for selection of two doses of GBP and three doses of VPA were in accordance to maximum human recommended doses (MHRD), i.e. 3600mg/kg/day and 2400mg/kg/day, respectively.

Neurohistopathological procedure

To record the neurohistopathological observations, half of the pregnant dams from each group were sacrificed after anesthetization with pentobarbitone on GD 21 at 0900 h, and their near term fetuses were collected by uterectomy and weighed. Fetal brains were dissected out by peeling the cartilage of skull carefully, washed with saline, then fixed by immersion in 10 % neutral formalin; and further processed for paraffin microtomy. The paraffin blocked were cut at 7 µm thin serial sections by rotatory microtome stained with H & E stain. These stained sections were identified with the help of stereotaxic atlas of developing rat brain (Altman and Bayer, 1995). The neurohistopathological microphotographs were captured by Eclipse CCD camera of Nikon 831. For measurements of thickness of typical layers of hippocampus, three fetal brains from each group were selected randomly, of which five consecutive sections were analyzed. Multiple observations of hippocampal thickness were analyzed with the help of Statistica- 10 software.

Neurobehavioural procedure and testing

Further, remaining 50% vehicle and drug exposed pregnant rats were allowed to deliver naturally. These newborn pups were culled (n=6 per group) postnatally, and reared with their biological mothers up to postnatal day 21(PND 21). After weaning period, male rat offspring were segregated into different cages (n=4 per cage) for social interaction up to PND 56.The offspring used in this study were weighed at birth, then once a week till 8 weeks of age.

These young rats were subjected to a neurobehavioural (cognition) test. All behavioral tests were performed between 09.00 to 11.00 hrs at noise free room.

In this study, T maze was used to test learning and memory performance. This paradigm was used to evaluate the cognitive function in rodents (Wahleston, 2011). The T-maze consists of two opposite arms 50×10 cm, crossed with two enclosed arms of the same dimensions with 40 cm height. The arms were connected with a central square (15×15 cm) to give the apparatus a 'T' appearance. The maze was kept elevated 55 cm above the floor in a dim light room, and food pellets were placed at the blind end of the enclosed arms. On day 1, individual food deprived rat was placed on distal end of the open arm facing toward the central square and time taken by the rat to locate the food pallets in the enclosed arms. On day 2, similar procedure was performed by the same rat to record the transfer latency. After an interval of one week i.e. on day 9, transfer latency of each rat was again recorded as the time taken to locate the food pellets present into enclosed arms. In this test situation, maximum 5 min time span was ascertained.

Statistical Analysis

All data were represented as mean and standard error (Mean ± S.E). The variables were analyzed using one way analysis of variance (ANOVA) followed by post hoc Tukey's multiple comparison test to determine difference amongst groups for hippocampal thickness and behavioral test. For all statistical values, alpha level was set at $p<0.05$. All calculations were done with the help of Microsoft Excel and Statistica-10 software.

RESULTS

One way ANOVA followed by Post- hoc Tukey's multiple comparison test displayed substantial reduction in total thickness of CA1 region of GBP exposed groups [$(F (2,15) =1999, p<0.001$] and VPA exposed groups [$F (3, 20) = 36385, p<0.001$]. On examination of thickness of different neuronal layers (polymorphic, pyramidal and molecular) of hippocampus, thickness of polymorphic layer was found substantially [$(F (2, 15) =1873, p<0.001)$] decreased in GBP and VPA [$F (3, 20) =2006, p<0.001)$] exposed groups. This decline was found at selected doses of GBP (42.28% and 40.15) and VPA (7.77%, 38.46% and 43.49%) in dose-dependent manner, respectively. The thickness of pyramidal layer was also found to be substantially diminished [$F (2, 15) = 5054, p<0.001$] in GBP and VPA [$F (3, 20) = 7785, p<0.001$] administered groups, and this reduction was also noticed at selected doses of GBP (63.84% and 72.71%) and VPA (11.84%, 30.56% and 52.55%) respectively, in comparison to control. Similarly, thickness of molecular layer was also found

to be substantially decreased [F (2, 15) = 7994, p<0.001] in GBP with 49.33% and 26.84% and in VPA [F (3, 20) = 2111, p<0.001] with 15.56%, 4.64% and 17.25% respectively, exposed groups at selected doses as compared to control. Overall, both GBP and VPA induced a dose-dependent reduction in all three typical layers of hippocampus and this impact was more pronounced in pyramidal layer than other layers.

On histopathological evaluation of GBP and VPA exposed fetal brain, the laminar architecture of typical three layered hippocampal cortex was found to be less developed, poorly differentiated and substantially reduced in size in all the exposed groups in comparison to vehicle treated (control) group. At higher doses of GBP and VPA, both polymorphic and molecular layers became intermingled into pyramidal layer; hence it was difficult to differentiate them. The cytoarchitecture of gyrus dentatus was also found to be poorly developed and differentiated in GBP and VPA exposed fetal hippocampus than respective control.

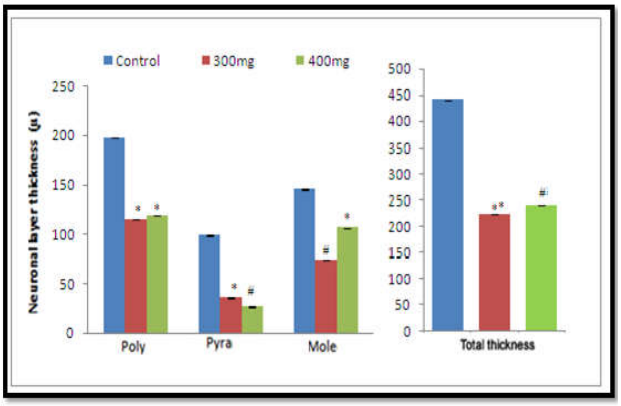

Fig.1 Effects of prenatal exposure to GBP on total and differential thickness of hippocampus of fetal brain. All data represent Mean ± S.E. value. * and # indicate level of significance at p<0.05 and p<0.001 respectively between control and AEDs exposed groups for ANOVA followed by post hoc Tukey's multiple comparison test. (Poly= Polymorphic layer, Pyra = pyramidal layer, Mole = Molecular layer)

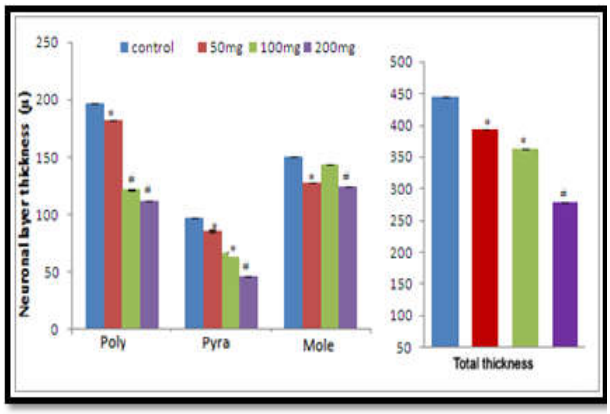

Fig.2 Effect of prenatal exposure to VPA on total and differential thickness of hippocampus of fetal brain. All data represent Mean ± S.E. value. * and # indicate level of significance, p<0.05 and p<0.001 respectively between control and AEDs exposed groups for ANOVA followed by post hoc Tukey multiple comparison test. (Poly= Polymorphic layer, Pyra = pyramidal layer, Mole = Molecular layer)

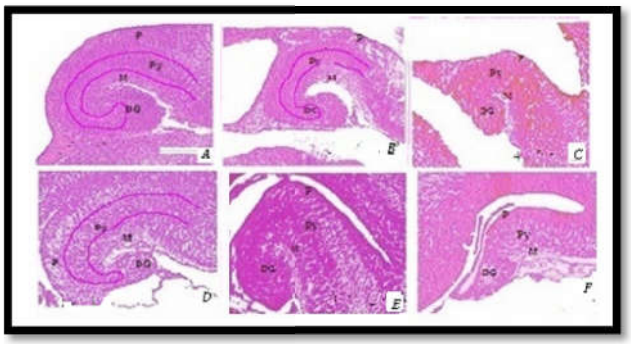

Fig.-3 Showing histopathological changes and cytoarchitectural pattern of hippocampus of control and prenatally GBP and VPA exposed fetuses (H&E staining). A. Control, B. 300 mg/kg GBP, C. 400 mg/kg GBP, D. 50 mg/kg VPA, E. 100 mg/kg VPA, F. 200 mg/kg VPA.

Effect of in utero exposure to GBP and VPA on cognitive T-maze

On day 1, vehicle treated control rats took significantly more time to locate the food placed into enclosed arms (from the distal end of the open arm) than time taken by the experimental rats prenatally exposed to GBP [F = (2, 36) = 1329, p< 0.001] and VPA [F = (3, 48) = 357, p< 0.001]. On day 2, control rats spent less time to find out the food pellets into enclosed arms than day 1(p<0.001), whereas GBP [F = (2,36) = 108.7, p< 0.001] and VPA [F = (3, 48) = 397.5, p< 0.001] treated rats took more time to search the food than control subjects. Furthermore, after one week of time interval i.e. day 9, control rats took substantially less time to locate the food stuff into enclosed arms in comparison to day 1 and 2, whereas prenatally GBP [F = (2, 36) = 433.8, p< 0.001] and VPA [F = (3, 48) = 1816, p< 0.001] treated offspring spent significantly more time in this task than control subjects (Figs. 4 & 5). It does appear that control rats took substantially less time to locate the goal on subsequent days 1, 2 and 3 which is an indicator of normal learning and memory state. Unlike to control, GBP and VPA exposed subjects spent almost equal time to locate the food in the enclosed arm, and couldn't learn from the previous tasks, that express the characteristic sign of impaired learning and memory.

From this experiment, it is also clear that GBP treated offspring could retain their cognitive performance than VPA treated rats on T maze.

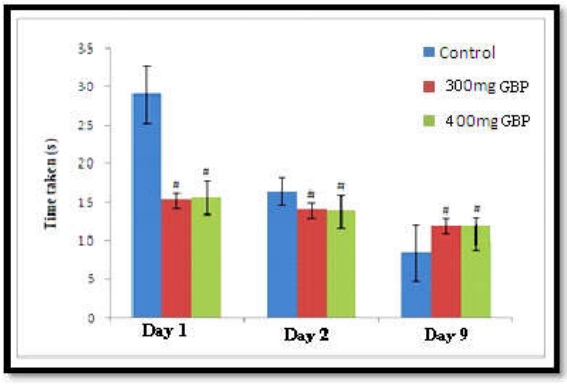

Fig.4 Effect of prenatal exposure of GBP on score of T- maze. * and # indicate level of significance, p<0.01, p<0.001 respectively between control and GBP exposed groups for ANOVA followed by post hoc Tukey's multiple comparison test.

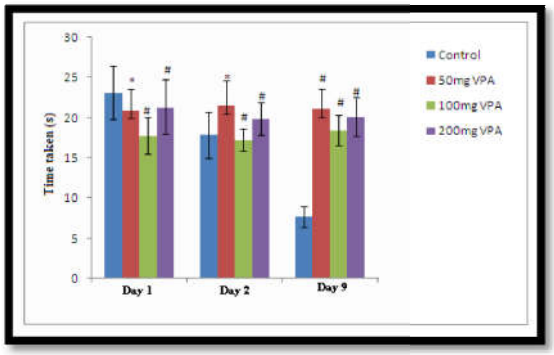

Fig.5 Effect of prenatal exposure to VPA on score of T- maze. * and # indicate level of significance at $p<0.05$ and $p<0.001$, respectively between control and VPA exposed groups for ANOVA followed by post hoc Tukey's multiple comparison test.

DISCUSSION

The present study revealed that prenatal exposure to GBP and VPA showed substantial neurohistopathological changes along with significant reduction in total and differential thickness of polymorphic, pyramidal and molecular layers in CA1 region of hippocampus and cognitive impairment in young-adult rat offspring in comparison to control.

This study is in agreement with those workers who have suggested that prenatal exposure to AEDs, pregabalin, topiramate, gabapentin, valproic acid and vigabatrin are associated to histopathological changes on central nervous system (Salih, *et al*., 2014; Hashish, 2014; Olayemi *et al*., 2014; Ikonomidou, *et al*., 2007). Manent *et al*., (2007) reported that fetal exposure to GABA-acting AEDs can induce hippocampal and cortical dysplasias. Maternal exposure to phenobarbital also reduced hippocampal pyramidal and granule neurons and disrupted hippocampal cholinergic neurotransmission (Ikonomidou & Turski, 2010). Olayemi (2014) revealed that chronic administration to GBP and carbazepine (CBZ) induced structural changes and increased numbers of degenerative neurons in the hippocampus.

Several investigators have postulated different potential inducing mechanisms like drug doses, exposure period, i.e. critical and vulnerable period of brain development and growth, low molecular weight of drugs, level of neurotransmitters, nerve growth factors (NGFs), oxidative stress etc., but none of the central mechanism has been determined so far, how does AEDs induce structural changes in the developing fetal brain.

There is increasing evidence that a number of neurotransmitters, including dopamine and serotonin, and possibly GABA can play a trophic role in regulating of brain growth and development, and a number of studies also indicate that early exposure to compounds that block dopaminergic and gabargic transmission may block cellular proliferation, neuronal migration or growth (Ikonomidou & Turski, 2010; Kolb & Gibb, 2011). Recent studies on CNS development showed that these neurotransmitters may serve as molecules that regulate specific aspects of cell proliferation, survival, migration, circuit formation and establishment of topography (Bittigau & Sifringer, 2002; Kolb & Gibb, 2011). It has been presumed that early disturbances in neurotransmitters' level may be coupled with changes in cellular energy metabolism which ultimately leads to functional disturbances in neurotransmitters (Marchi *et al*., 2001). Therefore, neurotransmitters might be a potent candidate to alter the process of neurogenesis in fetal brain. This laboratory has previously reported that prenatal exposure to certain neurotrophic agents, at equivalent to therapeutic doses, could induce neurostructural changes in different regions of fetal brain as well as psychopathological impairment in young-adult offspring (Singh *et al*., 2016; Singh & Tripathi, 2015; Singh *et al*., 2015; Singh & Gupta, 2014; Singh & Tripathi, 2014; Singh & Singh, 2002).

AEDs exposure during brain development may cause proapoptotic action due to reduction in synthesis of neurotrophins, including brain-derived neurotrophic factor (BDNF) and neurotrophins 3 and 4, as well as to reduced levels of the active phosphorylated forms of extracellular signal regulated kinase (ERK1/2) and protein kinase B (AKT) (Ikonomidou & Turski, 2010).

These kinases are key players in two major survival-promoting pathways, the MEKERK1/2 and the PI3 kinase-AKT pathways, both of which are activated by tyrosine kinase receptors upon binding of growth factors (Bittigau, *et al*., 2002). Such changes reflect an imbalance between neuroprotective and neurodestructive mechanisms in the brain that will likely promote apoptotic death. Interestingly, 17β-estradiol counteracted inactivation of the ERK1/2 and AKT pathways and, in doing so, conferred protection against apoptotic neuronal deletion following treatment with some AEDs (Asimiadou, *et al*., 2005). Induction of enhanced neuronal apoptosis is one of several neurochemical changes seen in animals exposed to AEDs early in life. Early exposure (P6) to phenobarbital resulted in long-lasting changes in the cortical proteome, with long-lasting changes in the expression of proteins involved in oxidative stress, apoptosis, astroglial response, energy metabolism, and neuronal function. These changes provide at least one mechanism by which early injury can have long-lasting impact on cortical function (Kaindl *et al*., 2008). Longer duration of treatment with phenobarbital resulted in reduced GABA receptor expression (Ruiz, Hamon & Verge, 1989), increased muscarinic receptor expression in hippocampus (Rogel-Fuchs, *et al*., 1992; Pick *et al*., 1993), and decreased cerebral glucose utilization (Pereira *et al*., 1990). In addition to these changes, hippocampal neurogenesis is impaired after early life exposure to phenobarbital (Stefovska, *et al*., 2008; Frankel *et al*., 2016). It would be particularly interesting to determine whether these changes would occur if the shorter duration of treatment were to be sufficient to induce these alterations, it would suggest that they may contribute to the adverse behavioral findings.

This was certainly compelling, because deficits in hippocampal neurogenesis had been linked to behavioral impairments in memory tasks (Saxe, *et al*., 2006).

Our findings also concluded that young-adult rat offspring prenatally exposed to VPA and GBP when subjected to a cognitive paradigm displayed learning and memory impairment. Drugs treated subjects could not maintain retention capacity of cognition on T-maze at least for one week in

comparison to vehicle treated subjects who had displayed better cognitive performances (transfer latency) in the similar test situation. It is also expected that when these offspring were subjected to a stressful or new environment, they found difficult to cope- up with new environment resulting in slower habituation with altered behavioural responses as previously reported by this laboratory during evaluation of neuro-psycho-teratogenic potential of CNS acting drugs (Singh & Tripathi, 2015; Singh *et al*., 2015; Singh & Gupta, 2014; Singh & Tripathi, 2014; Singh & Singh, 2002). The present study corroborates well with findings of some clinical studies which have reported increased risk of neurodevelopmental delay (speech and language) along with motor developmental delay as well as learning difficulties, including other behavioural problems like social interaction, fearfulness (increased emotionality) and poor concentration with hyperactivity in children whose mother had taken antiepileptic drugs therapy (lamotrigine, phenobarbital, phenytoin) during pregnancy in general and perinatal and/or postnatal developmental period in particular (Forcelli, 2011; Tomson & Battino, 2008; Kini, 2006; Vinten, *et al*., 2005; Dean, *et al*., 2000). The cognitive side effects can include impaired concentration (Froscher, *et al*., 2005), cognitive dulling (Coppola, *et al*., 2002), reduced IQ score (Sun, *et al*., 2008) and cognitive speed (Gomer, *et al*., 2007), and abnormal thinking (Froscher, *et al*., 2005).

The mechanisms of anatomical and behavioral abnormalities may well differ, because it appears that the highest risk of anatomical defects is from first-trimester AED exposure, whereas the highest risk of behavioral defects appears to be from exposure during the third trimester. One of the leading hypotheses of anatomical abnormalities involves oxidative macromolecular damage from free radicals formed as reactive intermediates of AED metabolism (Well, 1997). The second and third weeks (day 7-21) of pregnancy in rats appears to be most vulnerable to the action of CNS drugs, because this is the critical period for synaptogenesis, formation of specific neural circuits, rapid cell proliferation and functional maturation of dopaminergic and other neurotransmitter systems. Neurobehavioural dysfunctions due to *in utero* exposure to psychotropic drugs indicate that last week of gestation and / or lactation is the most sensitive period for inducing long-lasting effects in mammals (Scalzo & Holson, 1989; Zhang, *et al*., 1996).

Reports on brain biochemistry revealed that early neurochemical alterations in the CNS may lead to functional deficits, resulting in abnormal behavioral pattern in F1 progeny. It is generally accepted that central dopamine facilitates hyperactivity, locomotion and aggression whereas acetycholine (ACh) is responsible for cognitive performances (Blokland, 1995). Abnormal interactions between malfunctioning of cholinergic and other neurotransmitter systems may cause additive or even synergistic effects on cognition. In this regard, the role of histamine is gaining increasing attention (Passani, *et al*., 2000; Passani & Blandina, 2003), and many recent results indicate that the histaminergic system influences learning and memory by modulating the release of ACh (Passani, *et al*., 2000; Bacciottini, *et al*., 2001).

The role of other neurotransmitters during early stage of neuronal maturation, synthesis and release in pre or post synaptic receptors may also be considered. The exact cause of neurobehavioural disturbances of prenatally GBP or VPA exposed rat offspring has not been well established so far.

CONCLUSION

In conclusion, present study demonstrates that *in utero* exposure to GBP or VPA, at different selected doses, may induce substantive reduction in fetal hippocampal thickness, neurohistopathological alterations; and cognitive impairment in young offspring. Therefore, caution must be taken before prescribing GBP or VPA during short gestation period considering the windows of susceptibility during fetal development.

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