Anxiety and depressive effects of antiepileptics in animal models

Abstract

Aim: Cognitive impairment is frequently observed in epileptic patients. It has been seen that not only epilepsy but antiepileptic drugs also impair cognitive functions. The present study was undertaken to assess the effect of three anticonvulsants Levetiracetam (60 mg/kg, p.o.), Vigabatrin (100 mg/kg, p.o.) and Sodyum Valproat (50 mg/kg, p.o.) on anxiety and depression on animal models of rats.

Materials and methods: Elevated plus maze (EPM) and Forced swimming test- Porsolt tests (FST) were carried out after 12^{th} weeks of the lifes of rats those that took the three anticonvülsion therapy administration.

Results: The results of the present study indicate that none of the three antikonvülsan drugs taken in childhood period impairs anxiety and depression in adult hood.

Conclusion: To conclude, long term administration of Levetiracetam, Vigabatrin and Sodyum Valproat have no effect on the anxiety and depression at adulthood time if epilepsy does not exist.

Key Words: Antiepileptic drugs, childhood, anxiety, depression, animal study.

1.Introduction

Epilepsy and antiepileptic drugs (AEDs) therapy have deleterious effects on cognition in patients receiving them who suffer from memory deficits, learning disabilities and behavioural problems [1, 2].

Individuals without epilepsy depressive and anxiety disorders tend to occur to gether with a high frequency, and anxiety is often co morbid with depression in epilepsy [3]. It has been noticed that AEDs can also brings about untoward effect on cognition and behaviour [4]. The neurocognitive burden of epilepsy may even start before birth through in utero exposure to AEDs [5,6]. At therapeutic doses AED treatment disturbs memory formation, retantion and orientation in patients receiving polytherapy [4].

Among the established antiepileptic drugs barbiturates and benzodiazepines have demonstrated detrimental effects on cognition leading to decreased arousal and deficits in cognitive performance [7-8]. Phenobarbital has more cognitive and behavioural toxicity as compared to other antiepileptics. However, some of the newer antiepileptic drugs have been reported to have favourable cognitive and behavioural profile such as vigabatrine, gabapentin, levetiracetam, tiagabine [9].

When tasked with addressing comorbid depression and/or anxiety in patients with epilepsy, neurologists may attempt to rely on potential mood stabilization properties of AEDs such as carbamazepine, lamotrigine, oxcarbazepine and valproate[10]. Conversly, neurologists must be mindful of not exacerbating underlying psychiatric disorders with AEDs. These include levetiracetam and perampanel, both of which may contribute to increased anger, irritability, anxiety and depression in some patients [11, 12].

Accordingly, we sought to evaluate changes in depression and anxiety symptoms following the initiation of Levetirasetam, Sodyum Valproat and Vigabatrin in animal models.

2. Study and design

This study is conducted by the departments of Pediatrics and Pharmacology, and is performed at Behaviour Pharmacology Laboratory of The Pharmacology Department in Medical Faculty of XXXXXX University. All experimental procedures were conducted in accordance with national legislation and associated guidelines of care and use of laboratory animals in research and approved by the Local Ethical Committee (approval number: 2016/04/29).

The number of 80 Healthy Wistar albino, those were acquired from the Central Animal House, University College of Medical Sciences, University of XXXXXX, XXXXXX; were seperated from their mothers at the 24th day of birth and were included into the study. Animals were kept under standard laboratory conditions (12: 12 light–dark cycle; temperature at 22°C; 50–60% relative humidity; ad libitum access to food and water). These animals were housed in groups of 5 rats per cage 43cm×28.6cm×15.5 cm) each of which were numbered, weighed and marked with a nontoxic different color marker that was designated before and weekly after animals were allowed food and water until the time of the 12.th week postnataly. Final solutions of all drugs used were obtained by adding the desired dose of the drug to 120 mL of drinking water, as previously reported [13]. The dose was calculated on the evidence that rats drink on average 12 ml per 100 g in a day; this was further confirmed by checking the volume drunk by the rats, as previously described [14]. Water bottles were wrapped in silver foil to protect from light and solutions were freshly prepared and replaced daily.

2.1.Drugs and dosing schedule

Levetiracetam (Keppra 100mg/ml oral solution-UCB Pharma), Vigabatrin (Sabril 500 mg tablet-Sanofi Aventis) and Sodyum Valproat (Depakin oral solution 200mg/ml-Sanofi Aventis) were purchased from market. Tablets (after crushing) and oral solutions were dissolved in water. Drug treatment was given till the end of 12th weeks. Levetirasetam given

60mg/kg/day, Sodyum Valproat given 50mg/kg/day and Vigabatrin 100mg/kg/day show highest anticonvulsant effect in clinical practice. The doses of drugs were standardized on the basis of the previous publications [15].

Control and drug groups included 10 male 10 female rats. Hence, the following groups of rats were formed:

1. Control group: (no drug use)10 female (CF) 10 male (CM)
2. Levetirasetam group: 10 female (LF), 10 male (LM)
3. Vigabatrin groups:10 female (VF) 10 male (VM)
4. Sodyum Valproat group. 10 female (NF) animals, 10 male (NM)

The animals were brought to the Farmacology animal laboratory at 13.th week of live for the experiments. The animals were were housed in cages coated with polivinil chloride (PVC) and ad libitum access to food and water daily. The bottom of the cage was covered with 3 cm of corncob bedding, which was manually pressed to ensure even distribution. Experimental sessions were recorded using a video camera, the recordings were evaluated using a software (Ethovison XT 11.0, Noldus, Netherlands). All groups were tested in the following order: The Elevated plus maze test (EPM test) and Forced swimming test- Porsolt test (FST).

The intensity of light was 50 lux for EPM and 300 lux for FST, respectively. For all behavioral studies, mice were transported into the testing room from the housing facility at least 2 hr before testing. All tests were performed between 12: 30 and 16:30 p.m. to avoid circadian variation.

2.2. Elevated plus maze test

The apparatus was elevated 80 cm above the floor. It consisted of two opposite open arms (110 cm × 12 cm) and two opposite closed arms of the same size with walls 30 cm high. The arms were connected by a central square (12 cm × 12 cm). An animal was placed in the center of the maze facing an open arm. The number of entries into and the time spent in closed arm were scored for 5 minutes. The recordings were evaluated using a software (Ethovison XT 11.0, Noldus, Netherlands).The maze was thoroughly cleaned after each mouse was tested [16].

2.3. Forced swimming test (Porsolt forced swimming test)

Forced swimming test (FST) was performed as described originally by Porsolt [17]. The external testing area is a rectangular shaped area made of a glass with the dimentions of 70cm-30cm-30cm that contained 2 plexiglass cylinders (height 45 cm, diameter 25 cm) in it.

a) Pretest: 24 h prior to the experiments, the rats were individually placed in plexiglass cylinders containing water (22°C) up to 25 cm of the cylinder's height. Fifteen minutes later, the rats were removed to a 30°C drying room for 30 min.

b) Test: 24 h after the pretest the rats were placed in the cylinders and immobility was measured for 5 min. A rat was judged to be immobile when it remained floating in the water in an upright position and only made very small movements necessary to keep its head above water. Experimental sessions were recorded using a video camera for 5-min period and than the recordings were evaluated using a software (Ethovison XT 11.0, Noldus, Netherlands) with respec to the time spent as immobile.

The water of the steup was replaced between every two to four subjects.

3. Statistical analysis

All statistical procedures were performed using the Graphpad Prism 6.0vfor Mac OS X software (Graphpad Software, USA). Animal behavior was analyzed by one-way ANOVA followed by Bonferroni's *post hoc* test . All tests used were two-sided, and $P \leq 0.05$ was considered significant.

4. Results

4.1. Elevated plus maze test

During this test, time spent in the closed arms were scored for 5 minutes and the percentage of it was compared within all groups. The percentage of the time spent in closed arms in all groups were; C=88.48±3.500, CF=90.22±3.255, CM=86.74±6.361; L=89.08±2.953, LF=90.88±3.339, LM=87.27±4.994; V=87.00±3.495, VF=85.59±6.130, VM=88.42±3.682; N=91.96±2.207, NF=92.75±2.538, NM= 91.17±3.740. Values are means ± Std. error of means. The time spent in closed arms in drug groups had a similar number with the control group.

There were no significant difference between control and drug groups, and also female and male groups (P>0.05) (Fig. 1, 2).

4.2. Forced swimming test

The percentage of immobility times for each experimental groups were; C= 41.17±3.567, CF=36.54±4.385, CM=45.80±5.453; L=51.17±3.109, LF=47.92±3.599, LM=54.41±5.051; V=46.73±3.701, VF=44.75±2.651, VM=48.70±7.068; N=40.64±4.783, NF=37.12±4.871, NM= 44.17±8.374. Values are means ± Std.error of means. The percentage of the time spent as immobile in drug groups did not differ from the control group. There were no significant difference between control and drug groups and also female and male groups (P>0.05) (Fig. 3, 4).

5. Discussion

Psychiatric disorders are frequently encountered in patients with epilepsy and are generally considered as a consequence of the disease and/or its treatment; furthermore, some common neurobiological basis has been proposed [18-20]. Moreover, psychiatric comorbidity might influence the choice of antiepileptic drug therapy, the effectiveness of the treatment, and the patients' quality of life [21, 22].

Both clinical and animal studies have been performed in this field in order to define or find a correlation between these pathologies [23, 24]. In our study we aimed to question the effects of the 3 commonly used antiepileptics (Levetirasetam, Vigabatrin, Sodyum Valproat) on the most commonly seen psychiatric disorders depression and anxiety without the presence of epilepsy.

The presence of depressive symptoms has been found to have a negative effect on the severity of adverse events related to antiepileptic drugs in persons with epilepsy. For example, in a population-based study, persons with epilepsy and depressive symptoms compared with asymptomatic persons with epilepsy were found to endorse adverse events related to antiepileptic drugs of greater severity [25]. To date there are no data on whether depressive and anxiety disorders have a different effect on adverse events, whether a worse effect may result from the joint occurrence of depressive and anxiety disorders, or whether subsyndromic forms of depressive episodes have a lesser negative effect than clear-cut depressive or anxiety disorders. Kanner et al. [26] performed a study and the findings of this study demonstrated that patients with SSDE (subsyndromic depressive Episodes), MDE (major depressive episodes), anxiety disorders, or mixed MDE/anxiety disorders endorse worse antiepileptic drugs -related adverse events than asymptomatic patients. Exclusion from the antiepileptic drugs of the four psychiatric items that can be as well the expression of a mood and anxiety disorder did not change the findings obtained with the original instrument,

which demonstrates that the higher antiepileptic drugs scores in symptomatic patients were not a function of circular reasoning. According to them the severity of adverse events did not differ between patients with anxiety disorders and MDE. However, the adverse events worsened when the two disorders ocur together in patients with more than one type of anxiety disorder. The data from this study suggest that the presence of comorbid mood and anxiety disorders should be investigated in patients reporting frequent antiepileptic drugs-related adverse events.

Russo et al. [27] presented a possible new experimental protocol for the study of drug effects on the development of psychiatric comorbidity in epileptic animals, more specifically chemically kindled animals (pentylenetetrazol kindling), subjected to the chronic mild stress (CMS) model procedure. They also tested the effects of chronic lamotrigine (LTG) treatment, started before CMS and after kindling, on the development of psychiatric comorbidity in epileptic and nonepileptic control animals. Increased anxiety was observed in the elevated plus maze test, openfield arena test, cat-odor exposure test, and resident intruder test. Depression-like behavior was measured in the forced swimming test (FST), and an increased immobility time was found. Their data for the PTZ-kindled group are in line with increased anxiety. Our research conducted on non epileptic animals showed the 3 anticonvulsan drugs Levetirasetam, Vigabatrin, Sodyum Valproat had no effect on anxiety development.

Moseley et al. [28] had a clinical trial about lacosamide and their results suggest lacosamide was not associated with significant changes in depression and generalized anxiety when patients were examined aggregately. Based on their findings, lacosamide appears safe to use in patients with these mood disorders as in our animal study. Their results suggest that lacosamide does not cause clinically significant changes in depression or anxiety symptoms in patients without prior histories suggestive of depression or generalized anxiety.

Children with epilepsy have been reported to be at high risk for behavioural and psychiatric disorders in population based studies [29]. Elevated rates of depression, anxiety and suicidal attempts have been reported in adults with epilepsy and it is increasingly being realised that both depression and anxiety in youth with epilepsy are common but often unrecognized disorders [29, 30]. The mostly used anticonvulsans such as Levetirasetam, Vigabatrin and Sodyum Valproat had no effect on depression and anxiety seen in epileptic patients. Thereafter these psychiatric comorbidities may be assignable to epileptic seizures not antiepileptics. Perhaps some antiepileptic drugs have detrimental effects on cognition but not all [7, 8]. Like previous studies [27, 28] we demonstrated that some antiepileptic drugs (Levetirasetam, Vigabatrin, Sodyum Valproat) had no worse effect on depression and anxiety disorders.

The early identification and treatment of both conditions is crucial to minimize the risk for suicide and negative impact on quality of life. The reported frequency and severity of emotional and behavioural problems in children with epilepsy would suggest that a comprehensive epilepsy service should provide assessment and treatment of psychiatric problems and there should be regular monitoring of psychological adjustment of children with epilepsy.

6. Conclusion

Most antiepileptic drugs can be used safely in epileptic patients. Epilepsy itself is the major factor of behavioural and psychiatric disorders in epileptic patients more than antiepileptics.

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Figure 1. Elevated plus maze test results for anxiety measures.

Time spent in closed arms %. C= Control group, L= Levetiracetam group, V= Vigabatrine group, N= Sodyum Valproat group.

One-way ANOVA followed by Bonferroni's post hoc test ; p>0.05(non-significant)

Figure 2. Elevated plus maze test results

CF= Control Female group, CF= Control Male group; LF= Levetiracetam Female group, LM= Levetiracetam Male group; VF= Vigabatrine Female group, VM= Vigabatrine Male group; NF= Sodyum Valproat Female group, NM= Sodyum Valproat Male group. One-way ANOVA followed by Bonferroni's post hoc test ; p>0.05 (non-significant)

Figure 3. The percentage of the time spent as immobile the forced swimming test (FST)

İmmobility Time arms %. C= Control group, L= Levetiracetam group, V= Vigabatrine group, N= Sodyum Valproat group.

One-way ANOVA followed by Bonferroni's post hoc test ; p>0.05(non-significant)

Figure 4. The percentage of the time spent as immobile the forced swimming test (FST)

İmmobility Time arms %. CF= Control Female group, CF= Control Male group; LF= Levetiracetam Female group, LM= Levetiracetam Male group; VF= Vigabatrine Female group, VM= Vigabatrine Male group; NF= Sodyum Valproat Female group, NM= Sodyum Valproat Male group.

One-way ANOVA followed by Bonferroni's post hoc test ; p>0.05(non-significant).