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Review Article

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SCREENING MODELS USED FOR ANTI-EPILEPTIC ACTIVITY AND VARIOUS HERBAL SOURCES BENEFICIAL IN EPILEPSY: A REVIEW

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ABSTRACT

Epilepsy involves a group of problems that goes ahead of seizures. The commonness of the disease in developing countries is advanced than that in developed countries the causes of epilepsy embrace chemical imbalance such as low blood sugar or sodium, head injuries, drug abuse or with-drawl, alcohol withdrawal, stroke or conditions that affect the blood vessels (vascular system) in the brain, hardening of the arteries (atherosclerosis) in the brain, brain tumour, brain infection, such as meningitis or encephalitis and Alzheimer's disease. It is obligatory to explore for an antiepileptic agent that is highly effectual as well as secure in terms of drug related toxicity. The main aim of this review is to explore about epilepsy, types of epilepsy and some screening methods for anti-epileptic activity.

KEY WORDS: Epilepsy, Anti-epilepsy, Seizures, Screening methods.

INTRODUCTION

Epilepsy is a brain disorder in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally. Neurons normally generate electrochemical impulses that act on other neurons, glands, and muscles to produce human thoughts, feelings, and actions. In epilepsy, the normal pattern of neuronal activity becomes disturbed, causing strange sensations, emotions, and behavior, or sometimes convulsions, muscle spasms, and loss of consciousness. During a seizure, neurons may fire as many as 500 times a second, much

faster than normal. In some people, this happens only occasionally; for others, it may happen up to hundreds of times a day. Epilepsy may develop because of an abnormality in brain wiring, an imbalance of nerve signaling chemicals called *neurotransmitters*, or some combination of these factors. Researchers believe that some people with epilepsy have an abnormally high level of *excitatory neurotransmitters* that increase neuronal activity, while others have an abnormally low level of *inhibitory neurotransmitters* that decrease neuronal activity in the brain. Either situation can result in too much neuronal activity and cause epilepsy. One of the most-studied neurotransmitters that plays a role in epilepsy is *GABA*, or gamma-aminobutyric acid, which is an inhibitory neurotransmitter. Research on GABA has led to drugs that alter the amount of this neurotransmitter in the brain or change how the brain responds to it. Researchers also are studying excitatory neurotransmitters such as glutamate. The use of animal seizure models is essential in the discovery and development of new drugs for the treatment of epileptic seizures.[1] Epilepsy is among the most prevalent of the serious neurological disorders, affecting from 0.5 to 1.0% of the world's population.[2] Seizures can vary widely in their clinical presentation, depending on site, extent and mode of propagation of the paroxysmal discharge and hence now looked at as spectrum of clinically different varieties rather than a single disease.[3] Epileptic seizures often cause transient impairment of consciousness, leaving the individual at risk of bodily harm and often interfering with education and employment. Therapy is symptomatic in that available drugs inhibit seizures, but neither effective prophylaxis nor cure is available. Compliance with medication is a major problem because of the need for long-term therapy together with unwanted effects of many drugs.[4] Seizures also may be a toxic manifestation of the action of central nervous system (CNS) stimulants and certain other drugs. Seizures often occur in hyperthermia (febrile seizures are very common in infants); sometimes in eclampsia, uremia, hypoglycemia, or pyridoxine deficiency; and frequently as a part of the abstinence syndrome of individuals physically dependent on CNS depressants.[5]

TYPES OF EPILEPSY

I. Generalised seizures

1. Generalised tonic-clonic seizures (GTCS, major epilepsy, grand mal): It is the commonest, lasts 1-2 min. The usual sequence is aura--cry-unconsciousness tonic spasm of all body muscles--clonic jerking followed by prolonged sleep and depression of all CNS functions.

2. Absence seizures (minor epilepsy, petit mal): It is prevalent in children, lasts about 1/2 min. Momentary loss of consciousness, patient apparently freezes and stares in one direction, no muscular component or little bilateral jerking. EEG shows characteristic 3 cycles per second spike and wave pattern.

3. Atonic seizures (Akinetic epilepsy): Unconsciousness with relaxation of all muscles due to excessive inhibitory discharges. Patient may fall.

4. Myoclonic seizures: Shock-like momentary contraction of muscles of a limb or the whole body.

5. Infantile spasms (Hypsarrhythmia): Seen in infants. Probably not a form of epilepsy. Intermittent muscle spasm and progressive mental deterioration. Diffuse changes in the interseizure EEG are noted.

II. Partial seizures

1. Simple partial seizures (SPS, cortical focal epilepsy): It is lasts 1/2-1 min. Often secondary. Convulsions are confined to a group of muscles or localized sensory disturbance depending on the area of cortex involved in the seizure, without loss of consciousness.

2. Complex partial seizures (CPS, temporal lobe epilepsy, psychomotor): Attacks of bizarre and confused behaviour and purposeless movements, emotional changes lasting 1-2 min along with impairment of consciousness. An aura often precedes. The seizure focus is located in the temporal lobe.

3. Simple partial or complex partial seizures secondarily generalized: The partial seizure occurs first and evolves into generalized tonic-clonic seizures with loss of consciousness.[6]

Antiepileptic drugs (AEDs) often cause problems by dampening neuronal excitability and by altering underlying systems, which can lead to impairment of cognitive functioning within various neuronal subsystems. AED effects can be drug-specific and dose-dependent and may be (supra-) additive in drug combinations.[7] Natural products from folk remedies have contributed significantly in the discovery of modern drugs and can be alternative source for the discovery of antiepileptic drugs with novel structures and better safety and efficacy profiles. Now, various phytochemical and pharmacological studies have been carried out on these antiepileptic plants.[8]

SCREENING METHODS

There are various methods used for screening of anti-epileptic drugs and some methods are discussed here

1. Picrotoxin induced seizures

The anticonvulsant effect of *A. senegalensis* root bark aqueous extract was tested in the rats according to Vellucci method with some modifications (Vellucci and Webster, 1984). The standard convulsant agent, picrotoxin (PTX, 10 mg/kg i.p) was used to induce convulsions in the rats. Diazepam (DZP, 2 mg/kg i.p) was used as reference anticonvulsant drug for comparison. Rats of either sex were randomly divided into five groups of 10 rats(Mahomed and Ojewole, 2006). The positive control group of rats received diazepam (2 mg/kg, i.p) 20 min before picrotoxin (10 mg/kg, i.p) injection. The test groups were injected of (200, 300 and 400 mg/kg, i.p) doses of the extract, 30 min before picrotoxin (10 mg/kg, i.p) injection. Following induction of convulsions; the animals were observed for 30 min for signs of neurological deficits. Subsequent period of time for latency to first convulsion, time before onset of clonic convulsions and mortality percentage were recorded. Abolition of clonic convulsions during 30 min of observation was the criterion of anticonvulsant activity. Rats that did not convulse 30 min after injection of the picrotoxin were considered protected (Adeyemi *et al.*, 2010; Yemitan and Adeyemi, 2005).[9]

2. Maximal Electroshock (MES) Method

The maximal electroshock seizure pattern was induced in animals which were divided into three groups containing 6 mice each, by using a convulsiometer to give an alternating current of 150 mA for 0.2 sec. After 45 minutes of post dosing, mice was subjected to MES of 150 mA of alternating current from a convulsiometer for 0.2 sec through a pair of electrodes attached to each ear. The duration of the tonic hind limb extensor phase, clonic phase and the number of animals protected from convulsions was noted. Phenytoin in doses of 20 mg/kg p.o was be used as standard and test compound in dose of 200 mg/kg body weight.[10]

3. Chemically Induced Seizures

Pentylenetetrazol is a tetrazol derivative with consistent convulsive effect in a larger number of animal species like mice, rats, cats, primates etc. It is believed to act by antagonizing the inhibitory GABAergic neurotransmission10. This model was used to screen the anti-epileptic efficacy of Ganaxolone against petit mal epilepsy as Ganaxolone also acts through GABA-A receptor modulator mechanism. Rats were injected with Pentylenetetrazol (70 mg/kg, i.p) 30

minutes after test drug and standard drug (Sodium Valproate – 200mg/kg) and the occurrence of the first generalized clonus (repeated clonic seizures of the fore and hind limb lasting over 5sec. with an accompanying loss of righting reflex) or jerky movements were recorded during individual observation for 30 min.[11]

4. Effect on leptazole-induced convulsions in rats

All the animals were injected subcutaneously with 80 mg/ kg of leptazole in the loose skin over the back, 1 h after the administration of the extracts and the standard drug diazepam (2 mg/kg, i.p.). The animals were observed for a further 1 h and the presence or absence of convulsions was recorded. The occurrence of facial or forelimb clonuses for more than 5 s was taken as the convulsion threshold.[12]

5. Yohimibine model

Antagonism against yohimbine-induced seizures in mice is considered to be a model predictive of potential GABA-mimetic agents. In mice the test compounds were administered intraperitonially. 30 min prior to 45 mg/kg Subcutaneous route of yohimbine HCl. The animals are observed for the onset and number of clonic seizures for 60 min.[13]

6. Bicuculline test in rats

Seizures can be induced by the GAGAA-antagonist bicuculline and are antagonized by known anti-epileptics. Female Sprague-Dawley rats are injected i.v. with 1 mg/kg bicuculline. At this dose, a tonic convulsion appears in all treated rats within 30 s after injection. Test compounds are administered orally 1 or 2 h before bicuculline injection. Dose-response curves can be obtained. Percentage of protected animals is evaluated. *ED*50-values and 95% confidence limits are calculated by probit analysis.

Modifications of the method: Czuczwar et al. studied the antagonism of Nmethyl- D, L-aspartic acid-induced convulsions by antiepileptic drugs and other agents.[14]

7. Strychnine (STR) induced seizure

Strychnine is a powerful convulsant. The convulsantaction of strychnine is due to interference with postsynaptic inhibition that is mediated by glycine. Glycine is an important inhibitory transmitter to motorneurons and interneurons in the spinal cord. The test drug at the doses of 100 and 200 mg/kg, standard drug phenobarbitone sodium and vehicle control were administered 30 min prior to Strychnine (2.5 mg/kg). Sixty healthy and convulsion free

Swiss albino mice (20-25 g) were randomly divided into 10 groups (n=6). Then the treatment was started in similar manner as described above. Onset to forelimb clonic and tonic seizures was recorded. Mice that did not convulse 30 min after strychnine administration were considered protected.[15]

8. The CCTE (Computerized Cognitive Testing in Epilepsy) battery

A Microsoft Windows operating system, 1024x768 resolution and a sound card are required to run CCTE. Participants perform a single session, seated with headphones in front of a touch screen monitor connected to a notebook in a quiet surrounding. CCTE delivers task instructions and materials verbally via headphones, alongside with the same information in writing via visual display. In a short training phase, each participant receives the opportunity to practice using the touch screen, and volume of the headphones can be adjusted individually. CCTE consists of six tasks taking approximately 30 min to complete in total. These subtests refer to the following established neuropsychological paradigms.

1. The tasks digit span forward and backwards constitute the neuropsychological standard paradigm to assess working memory as the capacity to hold information in the mind and to make it available for further information processing.

2. In the focused attention task, a paradigm to assess speed of information processing is employed using sequences of simple calculations. Speed of information processing refers to how quickly one can react to incoming information, understand it, formulate and execute a response. This task also involves attention, working memory and decision making. Performance is affected e.g. by the neurotransmitter balance of the brain, by the organization of neural networks supporting the respective procedure, and by the efficiency of the frontal lobes in organizing and directing information flow. Brain lesions, toxic substances and a variety of medications, including anticonvulsants, can slow information processing which often accompanies cognitive decline.

3. The visuospatial memory subtest examines the ability of storing and reconstructing the initial spatial arrangement of visually presented information, which is necessary for remembering the location of objects as well as orientation and navigation within one's environment. Visual memory deficits are predominantly associated with lesions in the non-dominant mesial temporal lobe.

4a. The complex attention task refers to the paradigm of visual scanning as the ability to actively explore the visual surrounding and to find relevant visual information in a fast and efficient way, e.g. a particular object among other objects. This requires gaze control, fixation, controlling one's focus of visual attention and the ability to plan behavior systematically. Visual scanning deficits may result from a variety of brain diseases, neurotoxic substances and medications.

4b. In the task of incidental memory, the paradigm of unintentional learning is represented, which means the random reception of information occurring in one's environment. As this experimental paradigm contains the unexpected demand of recalling previously seen objects, it differs from intentional learning and refers to daily life memory demands.

5. The verbal learning task refers to the learning of semantically associated and unassociated word pairs, a traditional neuropsychological standard paradigm to assess verbal memory, introduced by Hermann Ebbinghaus (1850–1909) and used in a variety of neuropsychological memory test batteries (i.e. Wechsler Memory Scale). Here, a paired-associate presentation and retrieval of stimulus and response are given. Verbal memory deficits characteristically accompany lesions in the mesial temporal lobe structures of the dominant hemisphere.

6. The figural short term memory task represents a paradigm to assess working memory for figural material, as the capacity to store non-verbal information and to recognize it out of similar stimuli, a paradigm used in different neuropsychological test batteries. The course of subtests is controlled by a script directing the participant through the tasks without any external assistance. After some short instructions, each task is started by the patient himself. Immediately after completion, age-related results are displayed in raw values and z-scores and presented in graphic form. For followup examinations, the battery is available in two parallel versions, referred to as versions ''A'' and ''B'', comprising the same task structure but differing slightly in the presented words and pictures.[16]

9. **Hypoxic Stress-Induced Convulsions in Mice:**

The albino mice each weighing 25-30gm, were divided into seven groups of six mice each. Group one was given saline orally and served as the control; group two received 4 mg/kg of diazepam (i.p), group three received 50 mg/kg BM orally, group four received 50 mg/kg adenosine (i.p), group five received 50 mg/kg of theophylline (i.p), group six received 50 mg/kg of BM orally followed by 50 mg/kg of adenosine (i.p), and group seven received 50

mg/kg of BM orally followed by 50 mg/kg of theophylline (i.p). The mice were put individually into a glass container of 370 ml capacity for induction of convulsion. The container was air tight, so under these circumstances, the animal showed convulsions and then mortality due to hypoxia. The latency for convulsions and death was assessed for each animal.[17]

SOME PLANTS HAVING ANTIEPILEPTIC ACTIVITY

S.No.	Plant name	Family	Extract used	Reference
1.	*Euodia hortensis forster*	Rutaceae	Methanol	[18]
2.	*Globimetula braunii*	Loranthaceae	Ethanol	[19]
3.	*Rorippa sarmentosa* (DC.) Macbr	Brassicaceae	Ethanol	[20]
4.	*Cassytha filiformis L.*	Cassythaceae	Ethanol	[21]
5.	*Carissa edulis*	Apocynaceae	Hydro-alcoholic	[22]
6.	*Mitragynainermis*	Rubiaceae	Ethanol	[23]
7.	*Crinum ornatum*	Amaryllidaceae	Methanol	[24]
8.	*Commiphorakerstingii*	Burceraceae	Methanol	[25]
9.	*Hippocratea africana*	Celastraceae	Ethanol	[26]
10.	*Nerium oderum*	Apocynaceae	Petroleum ether, methanolic, aqueous	[27]
11.	*Passiflora foetida*	Passifloraceae	Methanol	[28]
12.	*Oxalis corniculata L.*	Oxalidaceae	Methanol	[29]
13.	*Benincasa hispida*	Cucurbitaceae	Fruit juice and aqueous	[30]
14.	*Jasminum grandiflorum*	Oleaceae	Hydro-alcoholic	[31]
15.	*Ricinus communis* Linn.	Euphorbiaceae	Ethanol	[32]
16.	*Pongamia pinnata*	Fabaceae	Petroleum ether	[33]
17.	*Acorus calamus* Linn	Araceae	Aqueous	[34]
18.	*Cyperus rotundus*	Cyperaceae	Ethanol	[35]
19.	*Newbouldia laevis*	Bignoniaceae	Aqueous	[36]
20.	*Pithecellobium dulce*	Fabaceae	Ethanol	[37]
21.	*Morinda tinctoria*	Rubiaceae	Petroleum ether	[38]
22.	*Crassula arborescens*	Crassulaceae	Methanol	[39]
23.	*Guettarda speciosa*	Rubiaceae	Ethanol	[40]
24.	*Enicostema axillare*	Gentianaceae	Cloroform and water.	[41]
25.	*Erythrina variegata L*	Fabaceae	Chloroform	[42]
26.	*Lantana camara* Linn	Verbenaceae	Ethanol	[43]
27.	*Tragia involucrata* Linn	Euphorbiaceae	Methanol	[44]
28.	*Careya arborea* Roxb	Lecythidaceae	Petroleum ether (PE), chloroform (CH), methanol (ME) and aqueous (AQ)	[45]
29.	*Wrightia tinctoria* (Roxb)	Apocynaceae	Ethanol	[46]
30.	*Croton zambesicus*	Euphorbiaceae	Aqueous	[47]
31.	*Prosopis Cineraria (Linn)*	Mimosaceae	Methanol	[48]

32.	*Saraca indica* Linn	Caesalpinaceae	Methanol	[49]
33.	*Bryophyllum pinnatum*	Crassulaceae	Aqueous	[50]
34.	*Annona senegalensis* Pers	Annonaceae	Aqueous	[51]

CONCLUSION

Many people with epilepsy lead productive and outwardly normal lives. Medical and research advances in the past two decades have led to a better understanding of epilepsy and seizures than ever before. Different medications and a variety of surgical techniques are now available and provide good control of seizures for most people with epilepsy. Apart from other treatment options include the ketogenic diet and the first implantable device, the vagus nerve stimulator, the herbal sources are the best option when severe adverse effect are concern. Research on the underlying causes of epilepsy, including identification of genes for some forms of epilepsy and febrile seizures, has led to a greatly improved understanding of epilepsy that may lead to more effective treatments or even new ways of preventing epilepsy in the future. To overcome with epilepsy, the people with epilepsy needs information and psychological and social support from the family as well as society. This review is to provide a compiled literature to the researchers to explore the various models and plants which can be efficiently used in the epilepsy.

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