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Current therapeutic approaches to epilepsy

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Abstract

With a worldwide frequency of around 1%, epilepsy is one of the most frequent neurological disorders affecting humans. It has been estimated that as many as 50 million people throughout the globe suffer from this condition. While many people's seizures are well managed with current treatments, around 25% of the overall population still suffers from them. Epilepsy treatment often centers on anticonvulsant medication, which may need to be taken indefinitely. More than 20% of people with epilepsy will develop chronic intractable (refractory) epilepsy. Because of this, combined treatment is required. However, polypharmacy is hampered by cognitive impairment and medication interactions, and only approximately 10% of individuals with refractory epilepsy seem to benefit significantly from it. Many novel pharmacological drugs have been developed in the recent two decades, allowing for more effective treatment of epilepsy. So extensive data has been acquired both chemically as well as pharmacological point of view. Primary care doctors and anyone caring for people with epilepsy may hopefully find this information useful. This means they need to be aware of the new possibilities.

Key-Words: Epilepsy, Seizures, Anticonvulsant drugs, Polypharmacy

Introduction

nerve impulses from a cluster of brain cells Treatments like electric shock and chemical convulsants may cause seizures in otherwise healthy brains, but these seizures are not considered epileptic.b) Epileptic when they happen for no apparent reason. About half a percent to one percent of the population suffers with epilepsy, making it a prevalent and often debilitating illness. There are more than 40 different types of epilepsy. Again on the rise, over 75% of those with epilepsy get their first symptoms before the age of 18. The distinctive manifestation of epilepsy, known as a seizure, is linked to the intermittent, high-frequency firing of impulses by a network of neurons. Abnormal discharges in one part of the brain may spread to other parts of the brain.

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The symptoms, which may vary from a momentary lack of concentration to a full-blown convulsive fit lasting several minutes, are determined by the location of the initial discharge and the amount to which it has disseminated.The impaired brain region's function determines the specific symptoms that manifest. Therefore, hypothalamic involvement triggers peripheral autonomic discharges, and reticular formation in the higher brainstem involvement induces unconsciousness1. Usually there is no recognizable cause (idiopathic), although it may be develop as a consequence of various kinds of brain damage, such as trauma, infection or tumour growths[2] Classification of Epileptic SeizuresEpilepsy is classified in several ways:

Clinical events (usually seizure type).

Classification of seizure types using solely EEG data is now the most extensively used approach. This classification system was first implemented in 1969 by the International League for the Elimination of Epilepsy (ILAE) and updated in 19811-.

I. Generalized seizures[2]	II. Partial seizures [2]	III. Unclassified epileptic seizures
A. Tonic–clonic seizures (grand mal) B. Tonic seizures C. Clonic seizures D. Absence seizure (petitmal) E. Myoclonic seizure F. Atonic seizures (astatic)	A. Simple partial seizures i) With motor signs ii) With somatosensory or special sensory hallucination iii) With automatic symptoms and signs iv) With Psychic symptoms B. Complex partial Seizures i) Simple partial onset followed by impairement of conciousness ii) With impaired conciousness on onset C. Partial seizures evolving to	

The fundamental processes that set off and spread seizures

There is seizure initiation phase and seizure propagation phase, when seizure activity begins in a localized area of cortex and subsequently spreads to neighboring areas. It has been hypothesized from research into experimental models of these epochs that two processes occurring simultaneously in aggregate neurons define the beginning phase.

High-frequency action potential bursts, andIntense synchronization

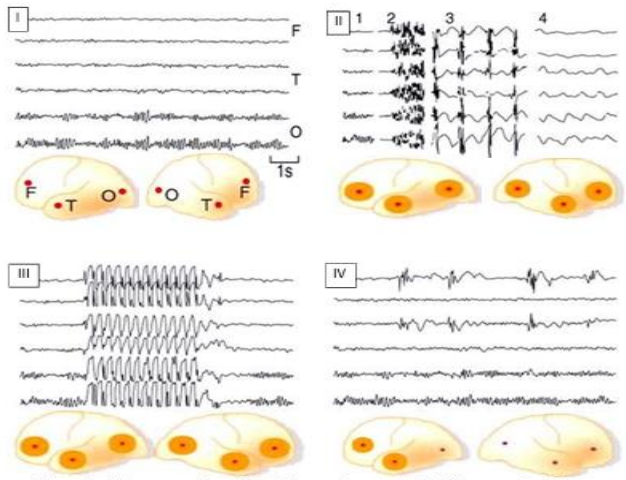

Fig. 1: Types of epileptic seizures. I. Normal; II. Generalized tonic-clonic seizures; III. Absence seizure; IV. Partial seizure.

Extracellular calcium (Ca2+) causes a sustained depolarization of the neuronal membrane, which in turn opens the voltage-dependent sodium (Na2+) channel, allowing sodium to enter the cell and generating repeating action potentials, or "bursting." A hyperpolarizing after potential, mediated by GABA receptors or potassium channels, then develops thereafter, depending on the kind of cell.The coordinated bursts from a significant number of synapses produce in a so called spike discharge on the EEG. The following is caused by the repetitive firing of neurons:A rise in extracellular potassium reduces hyperpolarization's effects and prevents the depolarization of neighboring neurons.Presynaptic terminals accumulate Ca2+, which stimulates neurotransmitter release.More Ca2+influx and neuronal activation occur as a result of depolarization-induced activation of the NMDA subtype of the excitatory amino acid receptor.Seizure activity may spread to neighboring areas via local cortical connection and to other regions of the brain via long commissural pathways, such the corpus callosum, if a significant number of neurons are recruited. Epileptogenesis

Epileptogenesis refers to the transformation of normal neurons network into one that is chronicallyhyperexcitable. For example, there is often a delay of month to year between an initial injury such as trauma, stroke or infection and the first seizure. The injury appears to initiate a process that gradually lowers the seizure threshold in the effected region until a spontaneous seizure occurs. Pathologic studies of the hippocampus from patients with temporal lobe epilepsy (MTLE) are related to structural change in neuronal networks. For example many patients with MTLE syndrome have a highly selective loss of neurons within the dentate gyrus. In response, to the loss of neurons, there is recognition or “spouting” of survivingneurons in a way that affects the excitability of the network. Thus an initial injury such as head injury maylead to a very focal, confined region of structural change that causes local hyperexcitability.The local hyperexcitability leads to further structure change that evolves over time unit the focal lesion produces clinically evident seizures.Genetic cause of epilepsyThe genetic causes of a few epilepsy syndromes have recently been discovered. They are:Myoclonic epilepsy with ragged red fibres (MERRF) syndrome is associated with a mutation of mitochondrial lysine.Mutation in the cystation B give may cause another form of progressive myoclonus epilepsy.Mutation with gene encoding the B4 subunit of the acetyl choline receptor appears responsible for a frontal lobe epilepsy syndrome.Treatment of epilepsyAntiepileptics are agents used medically to control the epilepsy; these are the mainstay of epilepsy management. Extracellular calcium (Ca2+) causes a sustained depolarization of the neuronal membrane, which

in turn opens the voltage-dependent sodium (Na2+) channel, allowing sodium to enter the cell and generating repeating action potentials, or "bursting." A hyperpolarizing after potential, mediated by GABA receptors or potassium channels, then develops thereafter, depending on the kind of cell.

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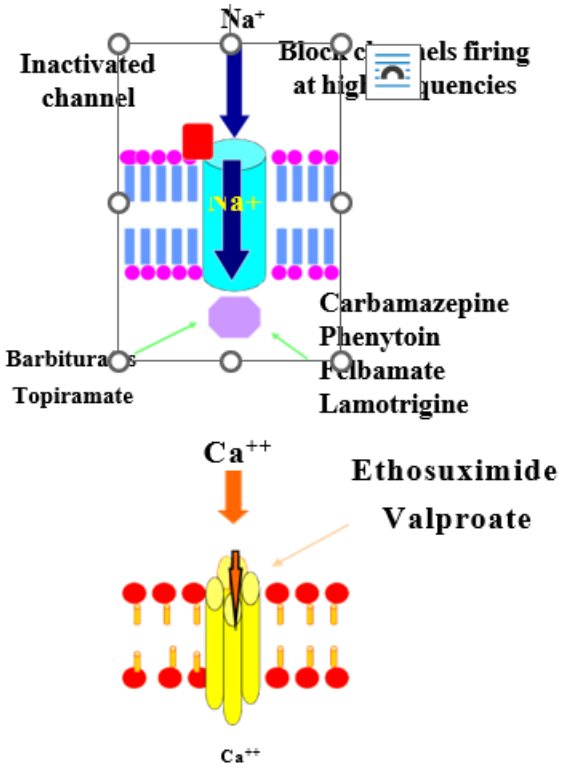
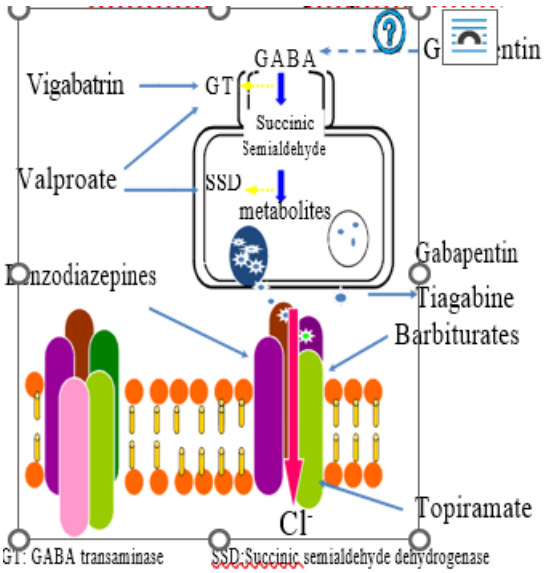
The Action of Anticonvulsants on the Central Nervous SystemPerhaps it shouldn't come as a surprise that antiepileptic medications might work in more than one way. Epileptic bursts include both Na+-dependent action potentials and Ca++-dependent depolarizing potentials, as discussed above in the processes of seizure mimicry and propagation. Several anticonvulsant medicines, including Phenytion, carbamazepine, oxcarbazepine, and lamotrigine, have had their mechanisms of action elucidated, and it has been shown that they all include the blockage of sodium channels.



Reduction in the flow of Ca^{++} through T - type Ca^{++} channels in thalamus

Since calcium channel activation mediates the depolarization seen in association with burst firing, this process is also the focus of much recent attention. Inhibiting T-type calcium channels seems to be the mechanism by which ethosuximide and similar anti-absence seizure drugs work.Due to synapses' crucial role in facilitating communication between brain cells, it was hypothesized that disruptions in this process may trigger convulsions. Pharmacological investigations of seizures provided support for the hypothesis that changes in synaptic activity, namely a decrease in inhibitory synaptic activity or an increase in excitatory synaptic activity, might cause a seizure. Most synaptic transmission in the human brain is mediated by amino acids; gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter, while glutamate is excitatory. Experimental animals have been shown to have seizures in vivo when given either an antagonist of the GABAA receptor or an agonist of a different glutamate-receptor subtype (NMDA, AMPA, or Kainic Acid). However, seizures may be reduced across models by

administering pharmaceutical drugs that increase GABA-mediated synaptic inhibition. Seizures induced by electroshock and chemical convulsants like pentylenetetrazole are two of the many seizure types that glutamate-receptor antagonists may prevent.



Several anticonvulsant medications on the market work by making GABA more effective. Both benzodiazepines and barbiturates, at clinically relevant concentrations, have an additive effect on GABAA receptor mediated inhibition.Viagabatrin, an anti-seizure medication, is believed to work by permanently blocking GABA transaminase, an enzyme that destroys GABA, hence raising brain GABA levels.Tiagabine's anticonvulsant effects may be due, in part, to its ability to increase GABA-mediated synaptic inhibition. It decreases GABA absorption by neurons and glial cells by blocking the GABA transporter, GAT-1.Therefore, antiepileptic medicines may inhibit action via any of the following pathways. Drugs like phenytoin, carbamazepine, and oxcarbazepine work by blocking sodium channels.

• Ethosuximide, valproic acid, and other T-type calcium channel inhibitors.

• Boosting GABA and other inhibitory transmitters (with benzodiazepines or barbiturates, for example).

Exitatory neurotransmitters like glutamate and aspartate are inhibited.

First, BARBITURATES:3,4

Barbiturate-independent anticonvulsant action.The barbiturate SAR is most active when the phenyl group at position 5 acts to raise the conductance of chloride ions, decrease the release of neurotransmitters in response to calcium, and provide GABA-like action.Generalized tonic-clonic seizures benefit from their usage in the clinic.

3. HYDANTOINS:3,4

Similar to barbiturates and cyclic ureides are these substances.They reduce calcium ion inflow during depolarization and resting sodium ion fluxes and currents flowing during action potentials.They work well for treating grand mal seizures.

Finally, IMINOSTILBENES3:

Carbamazepine and oxcarbazepine are linked chemically to the tricyclic antidepressants. They are modified iminostilbenes, with a carbamyl group replacing the second methyl group at position 5. Effective anticonvulsant treatment requires this moiety. Their effect seems to be a reduction in the speed with which voltage-activated Na+ channels recover from inactivation. Patients with simple and complicated partial seizures, as well as generalized tonic-clonic seizures, may benefit from them.

Four OXAZOLIDINEDIONES

By exchanging an oxygen atom for a nitrogen atom, these molecules are isoelectrically similar to the hydantoins.Anticonvulsant activity depends on the C-5 alkyl substitution. Against PTZ-induced convulsions, it provides excellent

protection. Absence seizures benefit clinically from their usage.

SUCCINIMIDES 1, 2, 4, and 5

The screening of aliphatic and heterocyclic amides demonstrated strong anticonvulsant efficacy among series of alpha n-substituted derivatives of succinimides. In thalamic neurons, these medicines decrease low threshold Ca2+ currents. The 3-Hz spike-and-wave rhythms characteristic of absence seizures are generated in large part by the thalamus. The seizures associated with petit mal epilepsy may be managed with these.

Valproic Acid, a member of the ALIPHATIC CARBOXYLIC ACID4 family

Chemically N-dipropylacetic acid (valproic acid) is a straightforward branched-chain carboxylic acid. Like phenytoin and carbamazepine, this effect seems to be mediated by a delayed reactivation of voltage-activated Na+ channels that were inactivated. To restrict continuous repeated firing, it also causes modest decreases in the low-threshold (T) Ca2+ current, an impact on T currents analogous to that of

ethosuximide in thalamic neurons. Valproic acid may be beneficial against partial and tonic-clonic seizures and absence seizures by lowering T currents and reducing the frequency of prolonged repetitive firing.

BENZODIAZEPINES3, NUMBER 7:

Many benzodiazepines have wide antiseizure characteristics, however they are predominantly used in therapeutic settings as sedative-antianxiety medications. But few of them are really authorized for long-term use against certain kinds of seizures. In the treatment of status epilepticus, both diazepam and lorazepam have established roles. Benzodiazepines' capacity to increase GABA-mediated synaptic inhibition underlies their anticonvulsant effects at non-sedative dosages.

8. RECENT MEDICINES:

Lamotrigine1,2:

Chemically Lamotrigine is chemically related to phenyltriazines. Lamotrigine inhibits partial and secondary generalized convulsions in the kindling paradigm and tonic hind limb extension in the maximum electroshock model, but not clonic motor seizures caused by pentylenetetrazol. Similar to phenytoin and carbamazepine, it inhibits recurrent neuronal activity and slows down reactivation of recombinant Na+ channels.

Gabapentin1:

It's made up of one GABA molecule attached to one lipophilic cyclohexane ring via covalent bonding. In the electroshock seizure model, it prevents the extension of the hind limbs during the seizure, and it prevents pentylenetetrazol-induced clonic seizures. Similar to valproic acid, but unlike phenytoin and carbamazepine, it performs well in these two tests. It is not understood how gabapentin works as an anticonvulsant. Weak hypotheses imply it may work by increasing GABA release from nonvesicular sources. When used with other anticonvulsants, gabapentin is beneficial for partial seizures with or without subsequent generalization.

Levetiracetam11:

A pyrrolidine derivative based on its chemical structure. Levetiracetam has a new pharmacological profile. In the kindling model, it prevents both focal and generalized tonic-clonic seizures, but it does not prevent seizures generated by maximal electroshock or pentylenetetrazol. However, it is unclear how levetiracetam achieves its anticonvulsant effects.Refractory partial seizures benefit from this treatment.

Tiagabine1,2:

It is a derivative of nipecotic acid. Tiagabine inhibits the GABA transporter, GAT-1, and

thereby reduces GABA uptake into neurons and glia. Tiagabine inhibits maximum electroshock seizures and both limbic and secondarily generalized tonic-clonic seizures in the kindling model this indicates its efficacy against partial and tonic-clonic seizures.

Felbamate 11:

Chemically it is a dicarbamate which is effective in both the maximal electroshock and pentylenetetrazol seizure models. Clinically relevant concentrations of felbamate inhibit NMDA-evoked responses and potentiate GABA-evoked responses. But it poorly controlled partial and secondarily generalized seizures. Topiramate1,2:

It is a sulfamate-substituted monosaccharide. Topiramate reduces voltage-gated Na+ currents. In addition, topiramate activates a hyperpolarizing K+ current, enhances postsynaptic GABAA-receptor currents, and also limits activation of the AMPA- kainate-subtype(s) of glutamate receptor. Topiramate inhibits maximal electroshock and pentylenetetrazol- induced seizures as well as partial and secondarily generalized tonic-clonic seizures in the kindling model. It is equivalent to valproate and carbamazepine in children and adults with newly diagnosed partial and primary generalized epilepsy. It also effective as amonotherapy for refractory partial epilepsy and refractory generalized tonic-clonic seizures. Zonisamide1,2 :

Zonisamide is a sulfonamide derivative it inhibits the T-type Ca2+ currents. In addition, zonisamide inhibits the sustained, repetitive firing of neurons, by prolonging the inactivated state of voltage-gated Na+ channels like phenytoin and carbamazepine. It is effective in refractory partial seizures.

Viagabatrin11:

It is relatively irreversible inhibitors of GABA-Transaminase (GABA-T), the major enzyme responsible for the metabolism of GABA in CNS. As a result of inhibition of GABA-T, there is an increase of concentration of GABA in brain as a result there is an inhibitory neurotransmission. It is mainly effective in partial seizures.

Conclusion

Even with the introduction of newer drugs, remaining more than thirty percent of patients is still need of an effective antiepileptic drug to control their seizures. Additional all presently Antiepileptic drugs only used as prophylactically, they do not cure or prevent the disease progression into refractory epilepsy. So, newer compounds are needed to cure the disease with betterunderstanding of mechanisms involved in epilepsy and also to solve the problems of development of resistant of drugs.

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