Biological Causes for Resistance to Antiepileptic Drugs

ESSAY

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LIST OF ABBREVIATIONS

5HT	Serotonin
ABCB1	ATP Binding Cassette Gene
Ach	Acetyl Choline
ACTH	Adrenocorticotropic Hormone
AD	Alzheimer's Disease
AED	Antiepileptic Drug
AHS	Ammon's Horn Sclerosis
AMPA	α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid
ANA	Anti Nuclear Antibodies
Apo E	Apolipoprotein E
ATP	Adenosine Triphosphate
BBB	Blood Brain Barrier
BCB	Blood Cerebrospinal Fluid Barrier
BCRP	Breast Cancer-Related Protein
BOLD	Blood-Oxygen-Level-Dependent
Ca^{2+}	Calcium
CA3	Cornu Ammonis
cAMP	Cyclic Adenosine Monophosphate
CBZ	Carbamazepine
cGMP	Cyclic Guanosine Monophosphate
CM	Centromedian Thalamic Nucleus
CNS	Central Nervous System
CO_2	Carbon Dioxide
COX-2	Cyclooxygenase
CPS	Complex Partial Seizures
CRH	Corticotropin-Releasing Hormone
CSF	Cerebrospinal Fluid
DNA	Deoxyribonucleic Acid
DRE	Drug Resistant Epilepsy
EEG	Electroencephalography
EPSP	Excitatory Postsynaptic Potential
FDG	Fluoro-D-Glucose
FeS	Iron-Sulfur
fMRI	Functional MRI
FMZ	Flumazenil
GABA	G-Aminobutyric Acid
GADA	Glutamic Acid Decarboxylase Antibodies
GCs	Granule Cells
GEFS+	Generalized Epilepsy with Febrile Seizures Plus
GluR	Glutamate Receptor
GM	Grand Mal
GTC	Generalized Tonic Clonic

HIV	Human Immunodeficiency Virus
HRQOL	Health-Related Quality of Life
HS	Hippocampal Sclerosis
IGE	Idiopathic Generalized Epilepsy
ILAE	International League Against Epilepsy
IQ	intelligence Quotient
JME	Juvenile Myclonic Epilepsy
K^+	Potassium
Ka	Kainate
LTG	Lamotrigine
MAPs	Microtubule-Associated Proteins
MDR1	Multidrug Resistance Gene-1
Mg^{2+}	Magnesium
MOA	Mechanism of Action
MRI	Magnetic Resonance Imaging
MRP	Multidrug Resistance-Related Protein
MTLE	Mesial Temporal Lobe Epilepsy
Na^+	Sodium
NF	Necrosis Factor
NINDS	National Institute for Neurological Disorders and Stroke
NMDA	N-Methyl-D-Aspartate
PB	Phenobarbitone
PCs	Pericytes
PD	Parkinson's Disease
PDS	Paroxysmal Depolarisation Shifts
PET	Positron-Emission Tomography
Pfn	Parafascicular Nucleus
P-gp	P-Glycoprotein
PHT	Phenytoin
PI	Phosphoinositide
QOL	Quality of Life
rTMS	Repetitive Transcortical Magnetic Stimulation
SCP	Slow Cortical Potentials
SE	Status Epilepticus
SMEI	Severe Myoclonic Epilepsy of Infancy
SMR	Sensorimotor Rhythm
SNP	Single-Nucleotide Polymorphism
SPECT	Single Photon Emission Computed Tomography
TGF-β	Tumor Growth Factor
TQD	Tariquidar
VNS	Vagal Nerve Stimulation
WADA test	Intracarotid Sodium Amobarbital Test
WHO	World Health Organization
Zn^{2+}	Zinc

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INTRODUCTION

Epilepsy is one of the most common paroxysmal and heterogeneous neurological disorders affecting over 42 million people worldwide with distinct symptoms, aetiology and prognosis. According to World Health Organiztion (WHO) estimate, worldwide eight per 1000 people have epilepsy. Despite the availability of several antiepileptic drugs, critical challenges remain in the treatment of epilepsy. Even after all possible therapeutic interventions, drug resistance has been reported in up to one-third of the patients.[1]

An important characteristic of drug resistant epilepsy is that many patients are resistant to several, if not all anti-epileptic drugs (AEDs). Based on several studies it was reported that patients who fail to respond to first-line or second-line AED therapy will develop drug resistance, even on using AEDs acting via diverse mechanisms. Drug-resistant epilepsy affects individual health and the quality of life, with heavy burden on society. Studies have shown that drug refractory epilepsy imposes serious threats to patient's life which include neuropsychological illness, psychiatric and social impairment, reduced marriage rates and decreased life span. Further, only a subgroup of refractory patients responds to surgery or other specialized treatments and make them seizure free but others will continue to have seizures. Identifying the factors that contribute to drug resistance is, therefore, a major challenge, with a potentially significant impact on clinical practice.[2]

Although more than 10 new antiepileptic drugs have been developed in the past decade, epilepsy remains resistant to drug therapy in about one-third of patients. Approximately 20% of patients with primary generalized epilepsy and up to 60% of patients who have focal epilepsy develop drug resistance during the course of their condition, which for many is lifelong.[3]

The continued occurrence of seizures despite the use of several antiepileptic drugs, even as polytherapy at maximal tolerated doses, is a major health problem and increases the risk of death from epilepsy. None of the reported associations with clinical drug resistance, such as remote symptomatic causes, early onset, multiple seizure types, and a high frequency of seizures before the initiation of treatment, provide a mechanistic explanation of the phenomenon. In addition, it is not clear why the same type of epilepsy may be drug-resistant in one person and drug-responsive in another and whether this is a pharmacogenomic phenomenon.[4]

The mechanisms underlying the development of drug-resistance in epilepsy are complex and, at this time, not fully understood.Drug-resistance depends on a number of clinical aspects including aetiology, early age at seizure onset, type of epileptic syndrome and seizure, structural brain abnormalities or lesions, or abnormal electroenceph-alographic findings. Furthermore, drug-resistance may depend on genetic and acquired factors affecting pharmacokinetics or pharmacodynamics of AEDs. Genetic factors may reduce serum drug concentrations

either by reducing absorption or by increasing elimination and/or the access of AEDs to the epileptic focus in the central nervous system (CNS). In addition, genetic factors may be responsible of changes in AED targets reducing the response to drugs.[5]

The plausible factors for drug resistance could be environmental and seizure related causes. But, there are reports conferring running of epilepsy among families, indicating a possible genetic cause for the disease. Genetic causes have gained attention for both epilepsy as well as drug resistance. For various cases, the causes and response to treatment are closely related. This holds true for various sodium channel mutations implicated in disease and also acting as novel targets for various AEDs. Identification of predictive markers for drug resistance may revolutionize the existing treatment strategies. There are reports about the associations between many genetic variations and clinical drug resistance; however, none of these associations has been unequivocally replicated. Two separate studies done in south and north Indian patients were also not able to find any evidence for association. Therefore, further exhaustive studies about the influence of genetic variations on drug resistance may be valuable.[2]

Epilepsy drug-resistance may depend on the metabolism of antiepileptic drugs (AEDs), transport to the epileptic focus and/or target sensitivity. Furthermore, drug response depends on multiple characteristics of the patient, the epilepsy, and the antiepileptic drugs used.[5]

The two well known hypotheses for understanding the biological mechanism underlying multidrug resistance are the target and transporter hypotheses. In target hypothesis, epilepsy-induced alterations in specific drug targets (reduction in sensitivity) such as sodium channels have also been a major cause for pharmacoresistant epilepsy. Transporter hypothesis suggests that increased expression of efflux transporter p-glycoprotein (P-gp), encoded by ATP binding cassette (ABCB1) gene, leads to decreased bioavailability and limited brain access of antiepileptic drugs that may result in drug resistance.[2]

An increased expression of protein drug transporters (for example, P-gp or multidrug resistance-related protein MRP) within the blood-brain barrier or in the epileptic focus itself seems an important mechanism of drug resistance. This leads to the enhanced removal of antiepileptic drugs from the brain and subsequently, their reduced concentrations in the target tissue. Also, mutations of genes encoding gamma-aminobutyric acidA (GABA-A) receptors or ion channels may be reasons for the diminished protection of antiepileptic drugs. Some role may be ascribed to the genetic polymorphism of liver microsomal enzymes. Last but not least, use of other drugs unrelated to epilepsy (i.e. theophylline) or ingestion of stimulatory substances (e.g caffeine) are likely to reduce the protective potential of antiepileptic drugs.[6]

Multidrug transporters such as PGP and MRPs are important gatekeepers in the blood brain barrier (BBB) and blood cerebrospinal fluid barrier (BCB), and there is increasing evidence

that over-expression of such multidrug transporters may be involved in the generation of pharmacoresistance in epileptic patients. If so, inhibitors of these drug transporters may prove useful in pharmacoresistant epilepsy. Inhibitors of PGP and, more recently, MRPs are currently clinically evaluated for reversal or prevention of intrinsic and acquired multidrug resistance in human cancer.[7]

Because drug resistance often occurs in a patient to multiple AEDs, if not to all the currently available AEDs simultaneously, the multidrug transporter hypothesis is considered in preference to alterations at specific drug receptor sites to explain the phenomenon of multi-AED resistance. However, the transporter and target hypotheses are not mutually exclusive; they may complement each other in the pathogenesis of AED resistance.[8]

It is hypothesized that seizure-induced alterations of brain plasticity including axonal sprouting, synaptic reorganization, neurogenesis and gliosis could contribute to the formation of abnormal neural network, which has not only avoided the inhibitory effect of endogenous antiepileptic system but also prevented the traditional antiepileptic drugs from entering their targets, eventually leading to drug resistant epilepsy DRE.[9]

AIM OF THE WORK

To review the underlying biological causes of resistance to antiepileptic drugs in order to prevent its occurrence and provide better control of seizures.

CHAPTER 1

Epilepsy is a cluster of disorders rather than a single disease. It affects about one in 200 people and may last a person's whole life. The individual, who suffers from epilepsy is vulnerable to economic, social and legal difficulties and might experience deep psychological problems. The goals of epilepsy management are to prevent discharges and to avoid their propagation. The understanding of the pathophysiology of the epilepsies is still incomplete.[10]

Definition of epilepsy:

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure. An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[11]

Epilepsy is defined as a condition characterized by *recurrent* (two or more) epileptic seizures, unprovoked by any immediate identified cause[12,13]. Multiple seizures occurring in a 24-h period or an episode of status epilepticus (SE) are considered a single event. Individuals who have had only febrile seizures or only neonatal seizures (seizures in the first 30 days of life), and

people with acute symptomatic seizures (seizures associated with acute systemic illness, intoxication, substance abuse or withdrawal, or acute neurological insults), and individuals with a single unprovoked seizure, are excluded from this category.

In some studies, "epilepsy" is defined as the above plus those with a single unprovoked seizure, any afebrile seizure, or febrile seizures.[14]

The WHO Neurosciences Research Protocol for studying the prevalence of neurological disorders in developing countries, which was developed in collaboration with the Neuroepidemiology Branch of the U.S. National Institute for Neurological Disorders and Stroke (NINDS)[15], defines epilepsy as two or more afebrile seizures unrelated to acute metabolic disorders or to withdrawal of drugs or alcohol. Patients who have had a seizure within the last 2-5 years and those on anticonvulsant medication are considered to have active epilepsy.[16]

Prevalence and incidence of epilepsy:

Epilepsy is one of the oldest conditions known to mankind[17] and still the most common neurological condition affecting individuals of all ages. At any given time, it is estimated that 50 million individuals worldwide have a diagnosis of epilepsy[18]. However, the heavy burden of this disease is not evenly distributed, and according to available data, there are disparities in