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Epilepsy: Pathophysiology and Matrix metalloproteinases and Its Management

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Abstract

Epilepsy affects 65 million people worldwide and entails a major burden in seizure-related disability, mortality, comorbidities, stigma, and costs. In the past decade, important advances have been made in the understanding of the pathophysiological mechanisms of the disease and factors affecting its prognosis. These advances have translated into new conceptual and operational definitions of epilepsy in addition to revised criteria and terminology for its diagnosis and classification. Although the number of available antiepileptic drugs has increased substantially during the past 20 years, about a third of patients remain resistant to medical treatment. Despite improved effectiveness of surgical procedures, with more than half of operated patients achieving long-term freedom from seizures, epilepsy surgery is still done in a small subset of drug-resistant patients. The lives of most people with epilepsy continue to be adversely affected by gaps in knowledge, diagnosis, treatment, advocacy, education, legislation, and research. Concerted actions to address these challenges are urgently needed. The blood-brain barrier is dysfunctional in epilepsy, thereby contributing to seizure genesis and resistance to antiseizure drugs. Previously, several groups reported that seizures increase brain glutamate levels, which leads to barrier dysfunction. One critical component of barrier dysfunction is brain capillary leakage. It is hypothesized that glutamate released during seizures mediates an increase in matrix-metalloproteinase (MMP) expression and activity levels, thereby contributing to barrier leakage.

Keywords: Epilepsy, pathophysiology, matrix metalloproteinases.

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1. Introduction

Over time, understanding of epilepsy's underlying pathophysiology has evolved from solely neuronal dysfunction to encompass more intricate mechanisms such as altered immune response, dysfunctional blood-brain barrier (BBB), glial dysfunction, and brain inflammation [1]. Matrix metalloproteinases (MMPs) play a significant role in remodeling extracellular matrix in various bodily processes and exhibit complex functions under normal and pathological conditions. They have been implicated in epileptogenesis, epilepsy progression, brain remodeling following seizures, seizure-induced cell death, BBB disruption, neuroinflammation, and abnormal synaptic plasticity [2]. Substantial evidence suggests that MMPs play a crucial role in increasing BBB permeability during brain insults, thereby promoting neuroinflammation. Among the MMPs, MMP-2 and MMP-9 are highly expressed in brain [3]. MMP-2 is believed to be involved in various neurodevelopmental processes. In addition, downregulation of MMP-2 has been proposed to inhibit BBB disruption and migration of inflammatory cells into central nervous system. Recent studies have demonstrated that seizures upregulate MMPs at BBB, leading to degradation of tight junctions and subsequent barrier leakage [2].

Therefore, downregulating MMP-2 may have neuroprotective effects in individuals with epilepsy. However, specific role of MMP-2 in epilepsy's pathogenesis is yet to be fully established. Consequently, MMP-2 holds potential as a biomarker for epilepsy when assessing human serum [2]. MMPs play a crucial role in remodeling pericellular environment by cleaving extracellular matrix (ECM) proteins. This family of enzymes, comprising over 20 members, requires Zn2+ for activation. Certain MMPs, including those anchored to cell membrane (e.g., MMP-11, MMP-14, MMP-15, and MMP-16), undergo intracellular activation via a furin motif before being transported to extracellular regions. Activation of other MMPs involves extracellular proteolytic processing of secreted zymogens by MMPs or specific proteinases [2]. Tissue inhibitors of metalloproteinases (TIMPs), a family of secreted proteins with multifunctional properties involved in growth promotion and cell cycle regulation, tightly regulate activities of MMPs.

During various stages of cerebellar development, MMPs and TIMPs exhibit region-specific and cell-specific expression profiles, contributing to processes such as granular cell migration, Purkinje cell arborization, and synaptogenesis.

The mechanisms governing MMP expression and activity are complex, involving posttranscriptional modifications, epigenetic processes, and regulation of gene transcription by various growth factors, cytokines, and chemokines [4]. MMPs also play physiological roles in neurogenesis associated with memory formation and emotion. The involvement of MMP-9 in emotion and cognition, potentially linked to activity-dependent synaptic plasticity and brain development. Furthermore, MMPs and TIMPs modulate pathophysiological functional and structural remodeling in tissues, primarily through the regulation of ECM protein cleavage, bioavailability of growth factors and cytokines, and shedding of membrane receptors. MMPs have been implicated in various pathological conditions of central nervous system, including ischemia, Alzheimer's disease, multiple sclerosis, Parkinson's disease, and malignant glioma. Altered regulation of MMP-2 and MMP-9 has specifically associated with several nervous system disorders. Therefore, understanding roles of MMPs in normal and abnormal brain functioning is a rapidly evolving area of research [5].

1.1. MMPs and their Implications in Epilepsy

Recent research has associated prolonged seizures with elevated serum levels of MMP-9 and an increase in MMP-9 to TIMP-1 ratio in individuals experiencing acute encephalopathy with blood-brain barrier dysfunction following prolonged febrile seizures. Cortical lesions in patients with focal cortical dysplasia type IIb and tuberous sclerosis complex, which are conditions causing chronic epilepsy in children, were found to exhibit elevated MMP-9 protein levels, suggesting a pathological role for MMP-9 in these treatment-resistant cases [4]. Another study discovered higher levels of MMP-9 in cerebrospinal fluid of patients with bacterial meningitis who developed secondary epilepsy compared to those who recovered without neurological deficits, implying that MMP-9 concentrations may contribute to postmeningitic neurological sequelae [6]. Given association of elevated MMP-9 levels with neuronal death, abnormal synaptic plasticity, and neuroinflammation during epileptogenesis, MMP-9 represents a potential therapeutic target for epilepsy. However, a recent study did not find statistically significant genetic associations between single-nucleotide polymorphisms in MMP-9 gene and temporal lobe epilepsy, suggesting factors influencing MMP-9 expression, activation, or inhibition might play a role in pathogenesis of temporal lobe epilepsy and other epileptic syndromes [6].

Certain chemicals, such as pilocarpine, PTZ, and kainic acid, can induce tonic convulsions and upregulate MMP-9 expression in rodents. Neuronal depolarization in the rat hippocampus has been shown to increase MMP-9 mRNA levels, with MMP-9 mRNA being transported to dendrites and synapses in the hippocampal dentate gyrus of rats treated with kainic acid. Following kainic acid-induced seizures, a decrease in MMP-7 protein and activity, particularly in the CA1 region of the hippocampus, was observed after 24 hours, while TIMP-1 protein levels increased in the hippocampus. Expression of TIMP-1 mRNA and protein in the hippocampus was quickly induced following seizures [7]. Additionally, significant upregulation of microglial TIMP-2 expression has been observed in dogs with seizures. TIMPs are produced by microglia and astrocytes in the cortex and white matter, where they may play a role in neural regeneration based on their expression profiles and the time after injury. While MMP-7, MMP-9, and TIMP-1 are expressed in response to neural activity in certain models of epileptogenesis, the precise pathophysiological and etiological roles of these metalloproteinases and their potential molecular targets remain unknown [4].

1.2. Epilepsy Diagnosis and Management

Various diagnostic tests are employed to determine the presence and specific type of epilepsy in individuals.

2. Imaging and Monitoring

2.1. Electroencephalogram (EEG)

Electroencephalogram (EEG) evaluates brain wave abnormalities, aiding in the assessment of potential benefits from antiseizure medications. Video monitoring, combined with EEG, helps identify seizure characteristics and rule out other conditions that resemble epilepsy, such as psychogenic non-epileptic seizures, cardiac arrhythmia, or narcolepsy. EEG is a fundamental tool in the identification of seizures and the characterization of seizure patterns and syndromes. Additionally, it aids in the selection of appropriate drug therapy and provides valuable prognostic information. For patients without a clearly defined diagnosis, ambulatory and video EEGs are recommended. These specialized forms of EEG monitoring help differentiate between nocturnal epilepsy and parasomnias, diagnose psychogenic non-epileptic seizures, characterize seizure types, quantify seizure frequency, and evaluate candidates for surgery [8].

2.2. Magnetoencephalogram (MEG)

Magnetoencephalogram (MEG) detects magnetic signals generated by neurons, aiding in the detection of surface brain activity abnormalities. MEG assists in planning surgical approaches to minimize interference with brain function while removing focal areas causing seizures [9].

2.3. Commonly used brain scans

- CT (computed tomography)
- MRI (magnetic resonance imaging)
- PET (positron emission tomography)

While CT can be used for initial diagnostic purposes, MRI offers superior resolution and provides detailed visualization of structural changes in the brain. Advanced techniques like multiplanar reconstruction further enhance the ability to identify lesions that may be missed by conventional methods. MRI has a sensitivity of 94% in detecting brain injuries related to epilepsy [5]. However, for some patients with epilepsy, neither EEG nor MRI can precisely identify epileptogenic focus. In such cases, further evaluation through interictal and ictal scalp EEG may be necessary. This invasive method involves placing electrodes directly on scalp to capture electrical activity during seizures. Another option is use of functional neuroimaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT). These imaging modalities utilize radiopharmaceuticals to assess alterations in blood flow in the brain and have proven to be valuable tools in localizing epileptic area [10]. CT and MRI scans reveal structural brain irregularities like tumors or cysts

that may trigger seizures. Functional MRI (fMRI) localizes normal brain activity and identifies functional abnormalities. Single photon emission computed tomography (SPECT) helps locate seizure foci in brain. PET scans identify brain regions with lower-than-normal metabolism after a seizure, indicating epileptic focus [11].

2.4. Metabolic work up

A metabolic work-up is essential in cases of refractory seizures, as they can be associated with various neurometabolic disorders. The underlying causes of epilepsy in these disorders may include energy deficiency, intoxication, impaired neuronal function, disturbances in the neurotransmitter system, or coexisting cerebral malformations [12]. Certain clinical indicators can guide pediatricians in considering a metabolic disorder and initiating further investigations. A metabolic work-up is recommended for children who are being considered for dietary therapies. The metabolic screen for suspected neurometabolic disorders should include blood gas analysis, arterial lactate, blood sugar, ammonia, and urinary ketones. Additional investigations should be tailored based on clinical suspicion. These may involve tandem mass spectroscopy, urine gas chromatography-mass spectrometry, assessment of long chain fatty acids (for peroxisomal disorders), evaluation of urine mucopolysaccharides/oligosaccharides, urine sulphite test (for sulphite oxidase deficiency), enzyme assays for lysosomal disorders, measurement of plasma/urine creatine, transferrin isoelectrophoresis (for congenital disorders of glycosylation), assessment of serum copper and ceruloplasmin (for Menkes disease), analysis of CSF sugar, lactate, and neurotransmitter profile, skin and muscle biopsies [12].

3. Treatment approach for epilepsy

The initial treatment approach for epilepsy typically involves monotherapy. If a satisfactory response is not achieved, two additional attempts at monotherapy may be made before considering combination therapy. In cases where seizures persist despite multiple drug combinations, surgical intervention should be evaluated. The effectiveness of polytherapy, when monotherapy fails, is approximately 10% [13]. Assessing the response to treatment requires considering the frequency of seizures. For individuals experiencing monthly seizures, it may take several months to determine the effectiveness of the drug. However, if seizures occur more frequently, such as on a weekly basis, a response to treatment can be evaluated within one or two months, and if improvement is observed, continuing treatment for a longer duration is recommended [10].

3.1. Antiepileptic drugs

Anti-epileptic drugs (AEDs) have diverse mechanisms of action, and some possess multiple mechanisms. While precise mechanisms of certain drugs are not fully understood, anti-seizure medications are typically categorized based on their primary mode of action. Below is a concise review of major AEDs on the market. Certain AEDs act on sodium channels by either blocking repetitive activation (phenytoin, carbamazepine) or enhancing slow inactivation (lacosamide). Others target calcium channels by blocking T-type calcium channels (ethosuximide, valproic acid) or N- and L-type calcium channels (zonisamide). Lamotrigine blocks sodium and N- and L-type calcium channels while modulating H-current. Topiramate blocks sodium channels, AMPA receptors, and inhibits carbonic anhydrase. Additional mechanisms include enhancing GABA-A receptors (phenobarbital, benzodiazepines), blocking NMDA receptors (felbamate), and opening neuronal potassium channels (ezogabine) [13].

3.2. Carbamazepine (CBZ)

Carbamazepine (CBZ) is indicated for focal and generalized seizures, bipolar disorder, and trigeminal neuralgia. By inhibiting the voltage-gated sodium channels, the CBZ reduces neuronal firing. Common side effects include the gastrointestinal upset, hyponatremia, rash, drowsiness, dizziness, blurred vision, and headache. Rare but serious side effects include the Stevens-Johnson syndrome, the toxic epidermal necrolysis, the leukopenia, and the aplastic anemia [13].

3.3. Oxcarbazepine

Oxcarbazepine has a similar mechanism of action to CBZ and is effective for focal and secondarily generalized tonic-clonic seizures. Side effects may include dizziness, headache, ataxia, nausea, rash, double vision, and hyponatremia [13].

3.4. Phenytoin

Phenytoin is one of oldest AEDs used for focal and generalized seizures and status epilepticus. It blocks sodium channels and has other mechanisms involving synaptic transmission, ionic gradients, and calcium-calmodulin phosphorylation. Major adverse effects include gingival hyperplasia, increased body hair, folic acid depletion, rash, and decreased bone density. Long-term usage may lead to confusion, ataxia, double vision, and neuropathy [10].

3.5. Lacosamide

Lacosamide stabilizes hyperexcitable membranes by inhibiting slow inactivation of voltage-gated sodium channels. It may also bind to CRMP2, implicated in epileptogenesis. Lacosamide is used for focal-onset seizures and is generally well-tolerated, with dizziness, ataxia, and nausea as common adverse effects. EKG monitoring is recommended due to dose-dependent PR interval prolongation [14].

3.6. Phenobarbital

Phenobarbital acts as a barbiturate, binding to GABA-A receptors and enhancing chloride influx for cellular hyperpolarization. It is used for generalized and focal seizures but has sedating properties that limit its use. It is a potent inducer of the CYP system, affecting serum levels of other drugs metabolized by this pathway [15].

3.7. Vigabatrin

Vigabatrin inhibits GABA transaminase, elevating GABA concentrations in the central nervous system. It is used adjunctively for refractory focal seizures and as monotherapy for infantile spasms. Patients should be cautioned about possible vision loss and may experience fatigue, dizziness, headache, and MRI abnormalities [13].

3.8. Topiramate

Topiramate has multiple modes of action, including sodium channel blockage, GABA transmission enhancement, NMDA receptor antagonization, and modest carbonic anhydrase inhibition. It is used for various seizure types and can cause weight loss, impaired cognition, expressive language difficulties, fatigue, depression, headae, paresthesias, metabolic acidosis, and kidney stones [16].

3.9. Valproate

Valproate is a broad spectrum medication for focal and generalized seizures. It inhibits sodium channels, augments GABA concentrations, and mildly inhibits T-type calcium currents. It should be used cautiously in hepatic insufficiency and avoided in urea cycle disorders due to the risk of hyperammonemia. Side effects include nausea/vomiting, tremor, weight gain/insulin resistance, metabolic syndrome, subclinical hypothyroidism, acute hepatocellular injury, and acute pancreatitis. It is contraindicated during pregnancy [17].

3.10. Levetiracetam

Levetiracetam's precise mechanism is not fully understood but involves binding to SV2A. It is used adjunctively for focal-onset seizures, myoclonic seizures, and primary generalized tonic-clonic seizures. It is well-tolerated, with common adverse effects being behavioral disturbances, drowsiness, dizziness, and upper respiratory infections. It is metabolized independently of the hepatic CYP system and does not require a prolonged titration period [18].

3.11. The ketogenic diet

Apart from AEDs, there are alternative treatments available for refractory epilepsy. The ketogenic diet is a low-calorie, high-fat diet that aims to induce a state of ketosis, resulting in antiepileptic effects. It is particularly effective in children and adolescents, as their brains can adapt to this form of metabolism. This dietary approach is recommended when drug therapy fails to provide adequate seizure control in children with multiple refractory seizures. The ketogenic diet has shown positive results in myoclonic, atonic, generalized tonic-clonic, focal, and absence seizures. However, it can give rise to complications such as hypoglycemia, excessive ketosis, diarrhea, reduced appetite, thirst, drowsiness, dehydration, metabolic acidosis, hyperuricemia, and hyperlipidemia. Regular monitoring of relevant laboratory parameters is essential [19].

3.12. Vagus nerve stimulation

Vagus nerve stimulation (VNS) is a minimally invasive alternative treatment for refractory epilepsy. It involves the implantation of a pulse generator, similar to a pacemaker, beneath the skin below the clavicle. The precise mechanism of action of VNS is not fully understood, but it is believed to activate neural pathways from the nucleus of the solitary tract to the limbic forebrain, resulting in the release of noradrenaline from the locus coeruleus and serotonin from the dorsal raphe nuclei in the telencephalon and diencephalon [20]. The pulse generator is programmed using a computer, and stimulation typically commences two weeks after surgical implantation. While most patients experience a reduction in seizure frequency, improved cognition, enhanced quality of life, and reduced depression, complete seizure control is rarely achieved. Common side effects include hoarseness, coughing, and pharyngeal paresthesia due to the intensity of the stimuli [20].

3.13. Epilepsy surgery

Epilepsy surgery is a well-accepted treatment modality for medically intractable epilepsy. However, the number of surgeries performed is lower than the potential number of surgeries, indicating underutilization of this treatment option [10]. Determining medical intractability is a subjective assessment. Typically, if the first antiepileptic drug fails to provide adequate seizure control, the likelihood of success with subsequent drugs decreases to less than 20%. After a second failed trial, the chances of future medication success drop to less than 10%. Given the availability of numerous antiepileptic drugs, it is not necessary to exhaustively try all options before considering surgery. Surgery should not be viewed as a last resort but rather as a viable treatment option after a reasonable trial of two to four major drugs [13]. For surgery to be considered, a patient's seizures must significantly impact their quality of life. The decision to undergo surgery requires an individualized risk-benefit analysis, where the potential benefits outweigh the potential complications. This analysis necessitates a comprehensive presurgical evaluation, including multidisciplinary assessments such as EEG-video monitoring, specialized magnetic resonance imaging (MRI) using an epilepsy protocol, and functional neuroimaging. Advances in imaging techniques have reduced the need for invasive EEG procedures [13].

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