DUSP4 Expression as a Therapeutic Approach for Epilepsy

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Epilepsy is a common neurodegenerative disorder and individuals of all races, genders, ages, social classes and geographies can be exposed to this condition. Seizures occur in epilepsy patients, and a persistent predisposition is evident. It is a brain disease characterized by neurobiological, psychological, cognitive, and social consequences of seizure relapses, as well as a recurrent state of seizures.[1] A "seizure" is a paroxysmal change in neurological function caused by excessive, hypersynchronous neuronal discharge in the brain. The term epileptic seizure distinguishes a seizure caused by abnormal neuronal firing from a non-epileptic event, such as a psychogenic seizure.[2] The characterization of alterations in stereotyped behaviors and recurring paroxysmal events is the fundamental cause of neural mechanisms that induce epileptic seizures.[1,3] The diagnosis of epilepsy covers a number of clinical situations characterized by temporary awareness and/or behavioral change. In practice, the diagnostic and electrical distinctive features of epilepsy may not be available interically in adults. If seizures occur infrequently, interictal epileptiform discharges may be present in those who do not have seizures.[4] Usually, the disorder can be diagnosed with a careful history or by observing a seizure.[1] Although an etiological agent can be identified, the cause of about half of the cases is still unknown.[5] A variable

ABSTRACT

One of the most common degenerative disorders of the neuronal system is epilepsy, a neurodegenerative disorder in which the individual suffers from categorized repetitive seizures in the brain and is linked to the development of various disorders or syndromes. Although the causes of epilepsy are unknown, it has been revealed that epilepsy is induced by the expression of several genes in the relevant molecular pathways. The mitogen-activated protein kinase (MAPK)-cyclic AMP (cAMP) response element-binding protein (CREB) signaling pathway is one of these pathways, and it is also the molecular basis of epileptic permanent seizures in the neocortex region of the human brain. By inhibiting the activation of MAPK, which is involved in the molecular organization of seizures in this part of the brain, the dual-specificity protein phosphatase 4 (DUSP4) protein functions as such an inhibitor. In this review, the roles of protein-based DUSP4, which serves as an inhibitor by reducing the actions of signaling pathways or molecules such as extracellular-signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK), in the molecular organization of epilepsy, epileptic seizures, and epilepsy were examined.

Keywords: CREB, DUSP4, epilepsy, MAPK, seizures

genetic predisposition to show epileptic seizures and the different distribution of certain environmental risk factors may explain the heterogeneity of the frequency, course, and consequences of the disease in the world.[1,6,7] Epilepsy is known to be the most common central nervous system (CNS) disorder.[8] At least 40% of all epilepsy worldwide has structural or metabolic causes as a result of various brain injuries. Infections, invasions, and seizures are examples of epilepsy with the most common risk factor.[9-12]

EPILEPSY-RELATED GENES

Epilepsy can be caused by primary genetic defects or subsequent to well-defined structural or metabolic diseases, some of which have genetic roots as well. More than half of all epilepsies are thought to be hereditary.[13,14] The use of genomic technology has had a significant impact on the discovery of

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the genetic basis of epilepsy and is predicted to play a key role in epilepsy diagnosis and therapy. Epilepsies caused by genetic anomalies, on the other hand, are extremely varied.[15] Because tuberculosis causes sclerosis, choosing mutations in some genes produces gross brain developmental anomalies in others (for example, tuberous sclerosis complex (TSC) mutations in the TSC1 and TSC2 genes).[16,17] Sodium voltage-gated channel alpha subunit 1 (SCN1A) mutations have been linked to epilepsy and have been identified as a common sign of febrile seizures.[18] Other genetic illnesses affecting the CNS, such as fragile X syndrome and myoclonus-dystonia, also cause seizures.[19]

According to the Online Mendelian Inheritance in Man database, 84 epilepsy-related genes have been identified and classified. As a result of mutations in these genes, pure or relatively pure epilepsies or epilepsies that are considered core symptoms occur. This category also includes genes that may be associated with multiple phenotypes other than epilepsy or seizures. However, an individual with mutations in these genes can only show epilepsy or seizures. For example, proline-rich transmembrane protein 2 (PRRT2) mutations are associated with various clinical syndromes such as paroxysmal dyskinesia, infantile convulsions with paroxysmal choreoathetosis, and benign familial infantile seizures.[20]

The epilepsy spectrum caused by gene mutations includes 23 epileptic phenotypes, ranging from a mild form of benign familial infantile seizures to an extremely severe form of early infantile epileptic encephalopathy. Multiple causal genes have been reported in 14 epileptic phenotypes. Early infantile epileptic encephalopathy was found to be associated with mutations of 42 genes. Progressive myoclonic epilepsy was associated with 11 pathogenic genes. However, with the exception of several cases with definitive one-to-one epilepsy-gene correlation, such as myoclonic-atonic epilepsy and solute carrier family 6 member 1 (SLC6A1), most phenotypes are generally expected to identify multiple genetic causes.[21] For example, cholinergic receptor nicotinic alpha 4 subunit (CHRNA4) was initially identified as the only pathogenic gene of nocturnal frontal lobe epilepsy, and subsequent studies have shown that cholinergic receptor nicotinic beta 2 subunit (CHRNB2), cholinergic receptor nicotinic alpha 2 subunit (CHRNA2) and potassium sodium-activated channel subfamily T member 1 (KCNT1) are also associated with this type of epilepsy.[22-24]

EPILEPTIC SEIZURES AND EPILEPSY SYNDROMES

Classification of epilepsy syndromes, epileptic seizures, and epilepsy examines previous International League Against Epilepsy (ILAE) classifications using modern terminology concepts. Epileptic seizures are divided into three major groups; i) Generalized seizures. They are divided into subclasses; absence, tonic-clonic (generalized tonic-clonic), myoclonic and atonic, ii) Focal seizures, iii) Epileptic spasms. The classification of epilepsies was previously based on initial regions (associated with a generalized or specific cortical localization) and etiology (symptomatic idiopathic). The updated system takes into account the expanding knowledge of structural and genetic causes and covers the degree of ictal semiotics (seizure type), diagnosis of the syndrome (if any), and functional impairment.[4,25]

GENERALIZED SEIZURES

Seizures can occur in the cortex or in subcortical structures. Generalized seizures begin to occur in bilateral distributed neuronal networks.[26,27] A focal seizure that occurs can turn into a generalized seizure. The subclasses of generalized seizures are mainly as follows; absence seizures, tonic-clonic, myoclonic and atonic. It's a form of absence seizure that involves nodding or winking, as well as inaction in the face of external verbal stimulation. It comprises bilateral symmetrical convulsive movements (hardening and subsequent twitching) of all limbs with unconsciousness in tonic-clonic seizures. Myoclonic seizures are characterized by rapid movements that are not caused by a specific neurological problem. They are also known as lightning seizures. One or more muscles may be affected by these short involuntary muscular spasms. As a result, myoclonic seizures might be localized or generalized. The most evident symptom of atonic seizures is that the person experiencing them loses their equilibrium and collapses. It's also characterized by muscle tone contractions that happen suddenly and for a short period of time all throughout the body.[2,4,28]

FOCAL SEIZURES

According to clinical findings, focal seizures are associated with the relevant cortex region. For example, a focal seizure caused by the occipital lobe may occur from visual phenomena; it can occur from the precentral gyrus with rhythmic clonic or tonic motor activity and postcentral gyrus with sensory

symptoms such as paresthesia. When consciousness is disturbed during a focal seizure, that is, when the patient is not able to respond normally to verbal or tactile stimuli, the seizure is classified as discognitive, i.e. complex seizures.[2]

EPILEPTIC SPASMS

One of the three types of seizures, epileptic spasms, has an unknown origin or cause. The rapid extension or flexion of the extremities is a symptom of epileptic spasms. It's held for a few seconds before being repeated in groups. Spasms associated with epilepsy can strike at any age. They develop a syndrome known as infantile spasms when they begin in the first year of life.[2]

EPILEPSY SYNDROMES

The International League Against Epilepsy classifies epilepsy syndromes as widespread and localized, idiopathic and symptomatic, etiology, genetic, structural/metabolic/autoimmune, and organized by starting age. More information about the many types of epileptic syndromes will be provided.[29]

SYMPTOMATIC AND IDIOPATHIC EPILEPSY

Idiopathic epilepsies are most probably triggered by such a combination of genetic and environmental factors (particularly epistatic and epigenetic influences in development), and while genetic factors are most likely to have a role, they have largely been proven hypothetically. There are numerous genetic causes of symptomatic epilepsy. At first look, the term symptomatic epilepsy may appear simple, however, this is not the case. For most of the 19th century, symptomatic epilepsy (also known as organic epilepsy) was overlooked as it was not seen through the eyes of actual epilepsy. By the middle of the 20th century, it had become axiomatic that all or almost all epilepsies were symptomatic, that is, epilepsy was a symptom of an underlying cause, even if the reason could not be determined. Because the definition of epilepsy has altered in recent history, the term idiopathic, which is in contradiction to much of it, has given new meaning to the term. For these reasons, the idiopathic term is more useful. Similarly, replacing the term symptomatic with structural/metabolic terms appears to be mostly superfluous, at least in terms of most symptomatic conditions.[29,30]

PROVOKED EPILEPSY

Epileptic seizures occurring in this group of epilepsy patients are triggered by provocation. Seizure provocation clearly affects genetic and acquired epilepsies, as well as focal and generalized epilepsies, and is difficult to map among traditional seizure types or syndrome classifications. However, it is largely unclear how it produces such seizures.[29]

ACQUIRED EPILEPSY

The term acquired epilepsy refers to symptomatic epilepsy that is not caused by genetic or developmental factors. Acquired epilepsy includes epilepsies due to external or environmental causes, as well as internal pathological processes that do not involve any major known environmental component (e.g. tumor, neurodegenerative disorders, autoimmune disorders). Non-systemic neurological disorders with no neuropathological findings are also excluded and categorized as provoked epilepsy.[31]

ACUTE SYMPTOMATIC EPILEPSY

Acute symptomatic epilepsy; "provoking factors" such as fever, metabolic disorder, alcohol include causes and acute brain injury. Since they are completely different in terms of physiology and clinical characteristics, it does not make sense to include both types of causes in a single category.[31,32]

LENNOX-GASTAUT SYNDROME

Lennox-Gastaut syndrome (LGS) begins to occur between the ages of one and six. Epileptic encephalopathy occurs in patients and they form seizures that are constantly developing medically (hundreds per day). Slow spike-wave EEG (electroencephalogram), mental radiation, and multiple seizure types are all features of LGS (e.g. tonic-clonic, atypical absence, atonic, myoclonic). Tonic seizures are seizures that occur mostly during muscle contractions and generally appear while sleeping. Atonic seizures, often known as fall attacks, occur without warning and frequently result in head or facial injuries. In children with LGS, atypical absences are common. Because there may be no improvement between epileptiform conditions that occur in protracted conditions such as preoccupation with any physical activity and sleepiness, it can be difficult to tell when a seizure terminates and when the next seizure will begin.[33]

Children with LGS are already neurologically

impaired. Many LGS etiology include hypoxic brain damage, cerebral dysgenesis, and neurocutaneous disorders. The encephalopathy in most children with LGS is stable, however, a degenerative condition such as neuronal ceroid lipofuscinosis can manifest as LGS. Children with LGS have such a poor neurological prognosis. Atonic, myoclonic, and atypical absence seizures may diminish over time, whereas tonic-clonic seizures and partial seizures may increase.[31]

In LGS patients, seizures are very resistant to anti-epileptic drugs (AEDs). Medication is individualized based on seizure type and frequency.[34] Some patients may be treated with clonazepam carbamazepine, topiramate, rufinamide, sertralin, clobazam, or felbamate. Due to the persistence of seizures, it tends to place patients in multiple AEDs. Drowsiness, exhaustion, nausea, ataxia, and rarely optimal seizure control are common side effects of this polypharmaceutical approach.[31]

LANDAU-KLEFFNER SYNDROME

Landau-Kleffner syndrome (LKS) (acquired epileptic aphasia) is a rare epilepsy condition in which a kid loses previously acquired language abilities of seizures or epileptiform abnormalities in the EEG. In its pure form, LKS occurs in children with normal language development who gradually lose the ability to understand spoken language and produce speech.[34] More recently, the syndrome has expanded to include behavioral and cognitive impairment, including autistic symptoms. The decline in social and language skills is common in children with autism with or without accompanying fits, so it can be difficult to differentiate autism and LKS. In LKS, compared to autism, social skills are better preserved. The pathophysiology of LKS is unknown. Imaging studies are often negative.[35]

CHILDHOOD ABSENCE EPILEPSY

Absence seizures, which are characterized by a reduction in responses, reactions, and vision, can occur in any epilepsy syndrome, including childhood absence epilepsy (CAE) and Juvenile myoclonic epilepsy (JME). The onset of CAE is between four and ten years of age. Seizures begin suddenly and usually last from five to 20 seconds. When the seizure ends, the patient immediately returns to his previous condition. As absence seizures are short and non-convulsive, they can easily be missed or misdiagnosed.[31]

The pathophysiology of seizures of absence involves the altered function of thalamocortical circuits. Thalamic relay neurons are abnormally ignited due to calcium channel dysfunction.[36] Ethosuximide and valproic acid are effective in the treatment of absence seizures.[37] Both drugs block low-threshold calcium currents in thalamic neurons.[38] CAE has a complex genetic basis, with only a few percent monogenically transmitted. The prognosis of CAE is normal, with 75% of children exceeding absence seizures during adolescence.[31]

METABOLIC, MITOCHONDRIAL, AND AUTOIMMUNE EPILEPSIES

The syndromes of epilepsy caused by metabolic, mitochondrial, and autoimmune have become more familiar and recognizable. Any changes in the energy metabolism in the neuron system can cause seizures. Some neurological impairments or neurodegenerative disorders occur as a result of the dysregulation function of auto-antibodies, and various cellular proteins trigger the formation of epilepsy, a neurological deterioration.[39-41]

THE ASSOCIATION BETWEEN EPILEPSY AND TUMORS

There is no definitive cure for epilepsy, and that is why individuals with epilepsy suffer from this neurological disorder for a lifetime. Brain disorders or degenerative conditions may not always trigger epilepsy, but once epilepsy occurs, epileptic circuits are stable in brain regions. By avoiding or preventing the spread of epileptic circuits, surgical approaches demonstrate a successful therapeutic strategy and the presence of endogenous mechanisms.[42]

Hereditary epilepsy has been more often associated with single gene defects in the receptors of ion channels and neurotransmitters.[43] However, these mutations occur as a very small part of epilepsy. In the most common form of epilepsy, seizures occur in an epileptic focus as a result of increased neuronal excitability, which is rhythmically depolarized. As seizures spread to the brain, they become more general. Any brain lesion can develop into an epileptic focus. Tumors are associated with epileptic seizures and are known as the most common symptoms. The incidence of seeing epilepsy in a patient with a brain tumor is linked to the tumor's morphology but can range from 30% to 100%.[43] Although most tumors have been associated with epilepsy, the most common are neuroglial tumors and gliomas. To a certain extent, dysembryoplastic neuroepithelial tumors (DNETs), gangliogliomas, low-grade glial

tumors, glioblastomas, metastases, leptomeningeal tumors, and primary CNS lymphomas have been associated with epileptic seizures.[43,44] Tumors that are characterized by or associated with epileptic seizures are symptomatic in nature and focal.[43] Depending on the localization of the tumor, semiological features, differences in tumor morphologies may occur depending on the course of the clinical picture of epilepsy.[13,43] Seizures may occur as the first symptom leading to the diagnosis of the tumor, and the risk of seizures is influenced by the type and localization of the tumor and the number of lesions.[43] Slow-growing tumors, particularly DNETs and gangliogliomas, are particularly epileptogenic and associated with the highest risk for seizures.[13,43] The location of the tumor is also important, for example, cortical tumors have a higher risk of causing seizures.[44] In addition, tumors in the frontal, temporal and parietal lobes have a higher risk of epilepsy compared to tumors in the occipital lobe. Multiple lesions were associated with a higher risk when compared with solitary lesions.[44] Infratentorial tumors are rarely associated with epilepsy.[43,44]

MOLECULAR CHANGES DUE TO ACTIVATION IN EPILEPSY

The ability of the human nervous system to reconstruct itself in response to environmental stimuli is a remarkable feature, especially in the early phases of development and childhood. This extraordinary feature of the brain, known as plasticity, is critical to its normal development and function. Plasticity helps with learning and memory and is implicated in epileptogenesis. The main method by which synaptic activity is transformed into structural alterations and connections is activation-induced changes in gene expression.[45] In some systems, it is estimated to be achieved by the direct activation of synaptic genes and the influence of neurotransmitter receptors and voltage-gated ion channels.[46-48]

Genetic research of rare forms of familial epilepsy involving voltage-gated and ligand-gated ion channels important in postsynaptic glutamate receptor development, as well as genes encoding scaffold proteins, has provided clues to the molecular architecture of human epilepsy. However, it has not been possible to calculate some of the rare cases that have been going on all this time. Patients with focal epilepsy who do not respond to drugs may benefit from selective removal of epileptic brain regions, implying that these areas are both necessary and

sufficient for disease manifestation. Genome-wide transcriptional profile of human epileptic neocortex removed after long-term in vivo electrical records has been shown in patients with medically refractory epilepsy, as an approach to understand what is unique about regions of the human epileptic cortex that tend to have seizures.[49,50]

The genome-wide transcriptome was then used to identify statistically significant molecular pathways enriched in epileptic brain regions and was then validated using human tissue samples. The most important of these are the pathways that activate CREB (cyclic AMP (cAMP) response element-binding protein) transcription through the MAPK (mitogen-activated protein kinase). The MAPK-CREB pathway and its downstream target genes are molecular pathways that then localize to large areas of sharply demarcated layer 2/3 neurons that show a marked increase in synaptic density. It has been established that human neocortical epileptic seizures are caused by focal brain regions with hyperconnected layer 2/3 neurons associated with persistent MAPK-CREB-mediated gene transcription.[51-53] Given this extremely important association of MAPK-CREB activation and CREB target gene induction in seizure initiation sites, this pathway is the cellular and spatial organization of the seizure-producing human neocortex.[49,54]

DUSP4 PROTEIN AND EPILEPSY

Dual-specificity protein phosphatase 4 (DUSP4) preferably inhibits extracellular-signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) signaling pathways.[52] Phosphatase activity and protein levels of DUSP4 are increased due to impaired proteasomal activity in senescent human fibroblast cells. 8-Bromo-cAMP (8-Br-cAMP) stimulation causes decreased proteasomal degradation of DUSP4 protein in Leydig cells.[53] DUSP4 stabilization leads to inhibition of ERK activity followed by reduced synthesis of the steroidogenic enzyme P450scc, which is critical for steroid synthesis.[55] DUSP4 is quickly stimulated after ERK activation.[56] ERK interacts with the DUSP4 protein on the remnants of Ser386 and Ser391 in the C-terminal and phosphorizes.[57] This leads to the prevention of DUSP4 from ubiquitin-mediated proteasomal degradation. The mechanism provides negative feedback control of ERK activity.[57,58] Consistently, a short added isoform of the human DUSP4 protein (encoding 303 amino acids), which lacks the MAPK binding site, is more susceptible to ubiquitination and proteasomal degradation than the

DUSP4 molecule.[59]

It has been discovered that the MAPK pathway is structurally activated in the lamina-specific alterations in the human epileptic brain.[50] The MAPK pathway is a cell proliferation and cell cycle progression mechanism that is found in all cell types throughout the body.[51,60-62] This shows that MAPK signaling can produce a positive feedback loop that maintains the epileptic circuitry, with frequent spiking occurring between seizures, also known as interictal spiking.[63-68]

Findings have been presented that a highly potent MAPK inhibitory protein called DUSP4 is an endogenous epileptic signaling inhibitor in the human neocortex. Through genomic techniques, DUSP4 was detected in a group of induced genes in the human epileptic neocortex that clustered independently of previously defined MAPK genes and proposed a different pattern of spatial expression. Consistently, small structures of DUSP4 mRNA expression have been identified in 2/3 layers of the epileptic human neocortex, which show a significant decrease in MAPK genes. In vitro DUSP4 acts as a powerful MAPK antagonist that is quickly and temporarily induced after repeated depolarizations and depends on MAPK signaling.[40,69] DUSP4 dephosphorylates the ERK signaling pathway and directly blocks the MAPK signal.[70] Over-expression of DUSP4 has been shown to result in a large reduction in MAPK signaling, as well as a considerable drop in ERK levels. In human neuronal-like cells, DUSP4 is thought to be a powerful inhibitor of MAPK signaling.[40,69,70]

Considering the remarkable inverse relationship between DUSP4 and early growth response 1 (EGR1)/dual-specificity phosphatase 6 (DUSP6) mRNA expression in the superficial cortical layers in the human epileptic cortex, it has been reported that there is an association between DUSP4 protein, MAPK signal, and frequency of epileptic spikes in the human neocortex.[40,71] Brain regions with high MAPK signals show high expression levels of both EGR1 mRNA and protein. These brain regions are defined as high and low MAPK signaling based on EGR1 expression in each patient. Interestingly, DUSP4 protein expression is significantly reduced in many of these same regions of high MAPK signaling and increases in these regions of low MAPK signaling.[40,57] When the DUSP4 protein is excreted at higher levels, both provide a functional correlation between reduced epileptic electrical activity and MAPK signal.[40,72]

In conclusion, epilepsy is a neurological disorder caused by recurrent seizures. Seizures occur when the structures of neurons in the brain create and send the wrong signal. Seizures that occur; muscle spasms, cognitive and behavioral impairments can be symptomatic, such as loss of consciousness. Since there is a possible interaction of many factors under epilepsy, a precise cause is unknown. Abnormality of brain development has been linked to causes such as brain injuries, deformation of their neuronal networks. Epilepsy occurs in the direction of recurrent seizures and there are types of seizures belonging to the disease. Epilepsy is connected with a variety of diseases and has been related to epilepsy because a variety of syndromes contain epileptic activity. Recurrent seizures occur as a result of brain damage, or these seizures cause extensive brain damage. One of these damages and the most common condition is tumor development in the brain. Epileptic seizures in the ion-gated channels of brain cells and as a result of a single gene mutation of neurotransmitter receptors spread to the unequal lobes of the brain, causing damage. Epileptic seizures, in fact, are one of the most prevalent symptoms of brain tumors. It is well understood that there is a link between brain tumors and epileptic seizures. It has been reported that MAPK, which is the signaling pathway that functions in the organization of the molecular basis of brain tumors, epilepsy, and cells, is active in the relevant loci of the brain where it carries out the CREB transcriptional activation pathway.

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