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Epilepsy and Migraine Shared Genetic and Molecular Mechanisms: Focus on Therapeutic Strategies

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Abstract

Epilepsy and migraine are both episodic disorders and share clinical as well as pathophysiological mechanisms. The prevalence of epilepsy in migraine patients is generally higher than normal as compared to general population and vice versa. Various environmental risk factors and genetic factors have been reported to be associated with susceptibility of these comorbid diseases. Specific genes have been implicated in the pathogenesis of the two diseases. However, the shared genetic susceptibility has not been explored extensively. Previous studies have reported that the alterations in the genes encoding ion channel proteins are common risk factors for both the diseases. The alterations in ion channel-encoding genes CACNAIA (T666M) and SCNIA (Q1489K and L1649Q) have been found to be involved in the development of familial hemiplegic migraine (FHM) as well as generalized epilepsy and some cases of focal epilepsy as well. The fact that both these disorders are treated with anti-epileptic drugs (AEDs) strongly supports common underlying mechanisms. This review has been compiled with an aim to explore the alterations in common genes involved in various pathways regulating neuronal hyperexcitability, a common risk factor for both these conditions. The avenue for future treatment strategies targeting common genes and molecular mechanisms has also been discussed.

Keywords Epilepsy · Migraine · Comorbidities · Genomics

Introduction

Migraine and epilepsy are both episodic neurological disorders having similar clinical features as well as pathophysiological mechanisms [1]. The prevalence of epilepsy in migraineurs substantially exceeds that of the general population [2], and the incidence of migraine headaches in patients with epilepsy is nearly twice in comparison with others without epilepsy [1]. There are evidences indicating that risk of migraine is increased significantly in patients with epilepsy as compared to general population and vice versa [3]. Patients with migraine are at a higher risk of developing epilepsy almost sixfold as compared to general population. Migraine is characterized by periodic attacks of throbbing pain on one side of brain along with symptoms including fatigue, nausea, hypersensitivity to light and sound, and temporary visual disturbances in some cases [4]. On the other hand, epilepsy is characterized by recurrent seizures due to abnormal brain activity, loss of consciousness, fear, anxiety, and severe headaches. Two main types of migraine are migraine without aura (MO) and migraine with aura (MA). Other subtypes of migraine include hemiplegic migraine and familial hemiplegic migraine (FHM). Epilepsies are classified as focal, generalized, combined generalized and focal epilepsy, and idiopathic.

Migraine aura-triggered seizure (migralepsy) is a complication and a rare condition in which an epileptic seizure is preceded by a migraine with aura attack. Conventional risk factors for migraine involve stress, tiredness, anger, smoking, and not getting enough exercise or sleep [5], whereas risk factors for epilepsy involve head trauma, brain conditions (brain tumors or stroke), infectious diseases, prenatal injury, and developmental disorders [6]. Most of these risk factors lead to the hyperexcitability of the brain.

Based on the outcome of epidemiological studies, epilepsy and migraine have been found to be comorbid conditions. The environmental and genetic factors have been reported to be significant risk factors for brain hyperexcitability. Although

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both epilepsy and migraine are individually influenced by genetic factors, the contribution of a shared genetic susceptibility has been evaluated to some extent. However, the mechanisms leading to co-existence of these two diseases remains unclear [1, 7–9]. Variations in genes encoding ion channel proteins have been found to be associated with the development of both the disorders. The fact that both these disorders are treated with anti-epileptic drugs (AEDs) strongly supports common underlying mechanisms [10]. Strong support for a shared genetic basis leading to FHM, an autosomal dominant syndrome, has been reported in severe migraine that occurs because of alterations in genes encoding ion channel proteins CACNAIA (P/Q-type voltage-gated calcium channel, T666M), SCN1A (voltage-gated sodium channel, Q1489K and L1649Q), and ATP1A2 (Na+-K+ ATPase, M721T and R689Q). T666M mutation in CACNA1A gene disrupts the Ca2+-binding sites in the pore [11], whereas Q1489K and L1649Q mutations in SCNA1A gene lead to the folding defects and thereby interfere with hydrophobic latch which block the ion pore [12]. The R689Q mutation in ATP1A2 gene affects the large intracellular loop between transmembrane domains M4 and M5, which harbors the ATP-binding and hydrolase domains and is implicated in several functions [13]. Alterations in all the three genes are also implicated in generalized and in some cases of focal epilepsy [14]. In epilepsy, neuronal hyperexcitability causes unusual hypersynchronous electrical discharge in neurons and further modifications in ion exchange process across membrane leading to recurrent seizures, while in migraine, hyperexcitability increases the extracellular concentration of glutamate (excitatory neurotransmitter) and thereby leads to cortical spreading depression (CSD), which further blocks the activity of neurons. There is tremendous efflux of K+ ions to extracellular compartments causing sustained depolarization followed by neuronal suppression. CSD activates trigeminal system releasing inflammatory molecules from the neurons and also suppresses the inhibitory function of GABA. Occipital lobe of brain is considered to be responsible for both the conditions because it is more prone to CSD. The threshold for onset of CSD in migraine is found to be lower than CSD in seizure. In addition the mutations in ion channels such as Na^+-K^+ ATPase pump have also been reported to be associated with both the disorders together [15]. Normally Na^+-K^+ pump regulates the extracellular concentration of accumulated K^+ ions by removing increasing glial Na^+-K^+ ATPase activity. The mutation in the sequence of α2 subunit of ATP1A2 gene has been found to be associated with FHM and benign familial convulsions in infants [16]. Mantegazza and Cestele (2018) reviewed extensively the pathophysiological similarities and differences between migraine and epilepsy [17]. They have concluded that these comorbidities might be generated on account of dysfunction in the common neuronal networks. The pathogenic mutations might target the same proteins but the dysfunction might be disease specific. There is a need to decipher the common pathological mechanisms leading to migraine and epilepsy. Therefore, the current review has been compiled with an aim to explain the common molecular mechanisms and pathways implicated in the pathogenesis of epilepsy as well as migraine. The genes involved in specific pathways altering molecular mechanistic aspects have also been discussed in detail.

Common Channel and CSD Mechanism

Migraine and epilepsy association is not a cause-and-effect relationship. Most likely they both are result of cortical neuron over-excitation. Epilepsy results from the synchronized discharge of neurons whereas migraine is associated with CSD, i.e., the strong depolarization of a large group of nerve cells or neuroglia that spreads to adjacent areas and inhibits neural activity [8]. Epilepsy and migraine can spontaneously induce CSD [18]. The results of the studies using animal models have suggested that many changes that occur during CSD (e.g., the increased release of glutamate, the increased concentrations of extracellular potassium ions, and the inhibition of the Na^+/K^+ ATPase) are also associated with the sense of prior prediction by some migraine patients [19–21]. Collectively these results indicate that CSD may be the basis for migraine with aura (Fig. 1). Further neocortical hyperexcitability is supposed to get transformed to abnormal hypersynchronous electrical discharges in epilepsy. Subsequent alterations in permeability of ion or ion exchange activity lead to recurrent seizures. However, in case of migraine, the neocortical hyperexcitability transits to CSD rather than the hyper synchronous activity in case of epilepsy. Action potential happening in neurons regulates all the activities of brain including epilepsy, which is a typical ion channel disease. Balance of synaptic excitation and inhibition controls the action potential in a neuron or group of neurons. This balance can be broken by GABA a principal inhibitor neurotransmitter and glutamate anomalies which may be the core of an excitatory neurotransmitter. Many mutations occurring in GABA receptor encoding gene or in calcium channel encoding genes result in idiopathic epilepsy that is generally inherited. These GABA and other channels regulate abnormal synchronization between cortex and thalamus and thereby lead to generalized spike-wave discharges. In addition, one of the significant common pathways of action potentials requires opening and closing of the voltage-gated sodium channels. Therefore, some idiopathic seizures result because of the alterations in sodium channel. The frequently used AEDs like phenytoin overpower the quick opening and closing of sodium channels. Another drug, topiramate, an antagonist at the AMPA-type glutamate receptor, weakens the carbonic anhydrase inhibitor, enhances the activity of GABA on chloride channel, and controls the

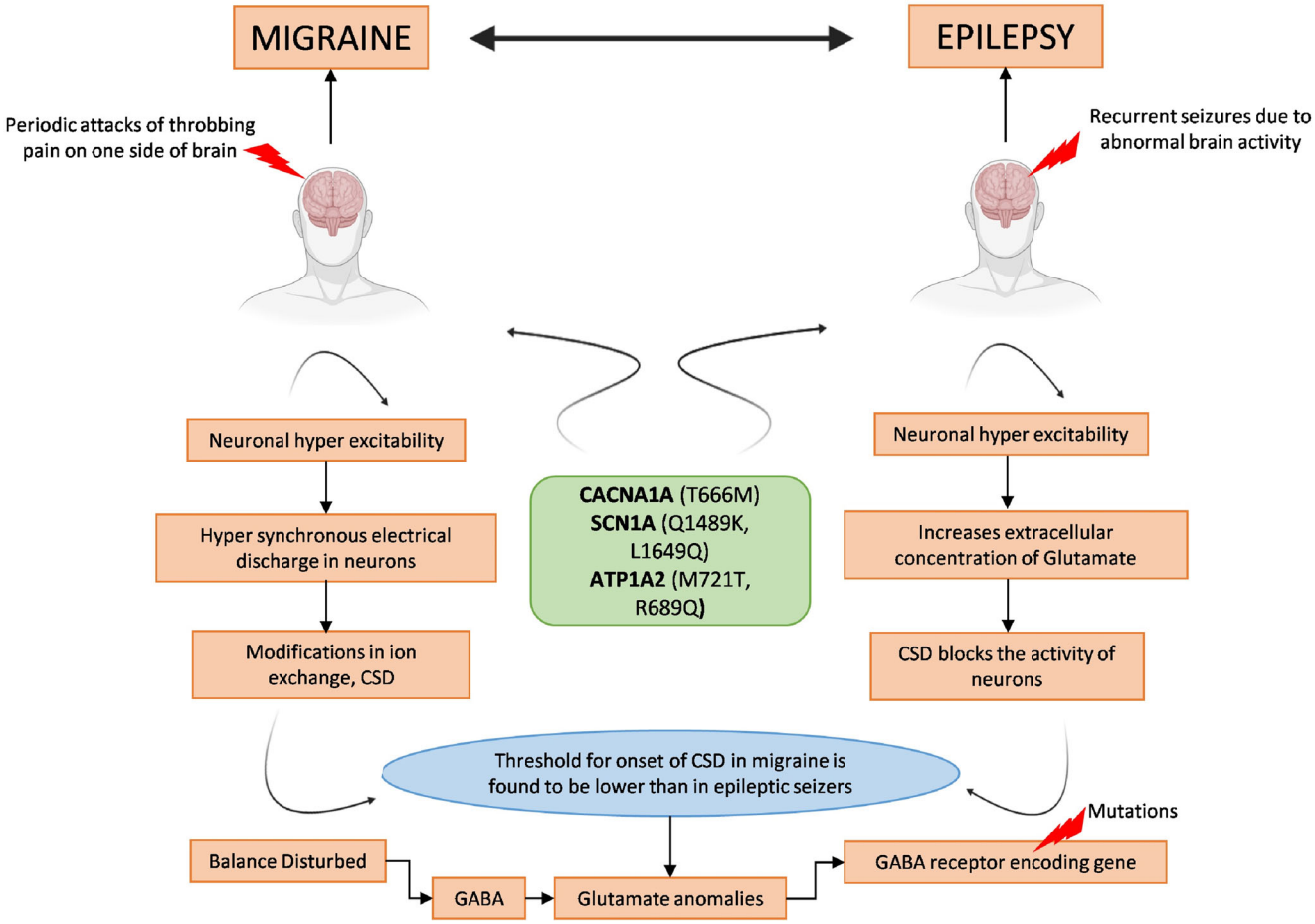

Fig. 1 Common molecular mechanisms shared by epilepsy and migraine: Both epilepsy and migraine are influenced by genetic factors, and these genetic factors are significant risk factors for brain hyperexcitability via the alterations in genes (shown in green) coding ion channel protein. Alteration in genes leads to unusual hypersynchronous electric discharge in neurons. Neuronal hyperexcitability causes modifications in ion exchange process across membrane leading to recurrent seizures in epilepsy whereas in migraine extracellular concentration of glutamate increases resulting a tremendous efflux of K+ ions, which further blocks the neuronal activity and thereby leads to brain hyperexcitability. Both these diseases can spontaneously induce CSD, making these as comorbid condition. CSD also activates trigeminal system and suppresses the inhibitory function of GABA. Balance of synaptic excitation and inhibition controls the action potential in a neuron or group of neurons. This balance can be disturbed by inhibition of GABA and glutamate anomalies (which may be the core of an excitatory neurotransmitter) or by mutations that occur in GABA receptor encoding gene. So, changes that occur during CSD lead to disturbance in balance

opening of L-type calcium channel. These anti-epileptic drugs are also found to be effective for migraine indicating that migraine might also result on account of changes in the ion channels [22].

Shared Genetic Factors Contributing to Migraine and Epilepsy

Both migraine and epilepsy are highly heritable especially idiopathic epilepsy and migraine with aura. The risk of patients with idiopathic epilepsy getting migraine with aura is approximately double [1]. Although there are hundreds of mutations causing monogenic type of both the diseases, but few shared genes involved in ion channel functions are responsible for co-occurrence of these (Tables 1 and 2). Mutations in the genes like CACNA1A (FHM1), ATP1A2 (FHM2), and SCN1A (FHM3) that causes familial hemiplegic migraine are also associated with epileptic seizures (Table 3). These three genes are involved in functioning of ion channels [42, 43]. The alterations in these cause dysfunction and hyperexcitability of neurons. CACNA1A gene codes for α-subunit of voltage-gated P/Q channels. Severe myoclonic epilepsy in infants is caused due to mutations in SCN1A gene [44]. SCN1A codes for the α-subunit of voltage-gated sodium channel Nav1.1. Another gene proline-rich transmembrane protein 2 (PRRT2) is responsible for modulating the release of neurotransmitter at synapses [45]. Alterations in this gene

Table 1 Common genes involved in epilepsy

Gene	Location	Function	Mutation	Impairment	Reference
KCNQ2 (potassium voltage-gated channel subfamily Q member 2)	20p13.3	Encodes for voltage-gated potassium channel subunits	853C>A (P285T), 740C>T (S247L), etc. are some of the mutations related to epilepsy (NEONATAL)	KCNQ2-related epilepsy has a pathogenic variant ("mutation") in the gene KCNQ2, which encodes the instructions to make a protein in the brain called a potassium channel. Pathogenic variants that affect the KCNQ2 potassium channel impair the flow of potassium ions in the brain	[23]
SCN2A (sodium voltage-gated channel alpha subunit)	2q24.3	Encodes for the voltage-gated sodium channel, neuronal type II, alpha subunit –Na(v)1.2	1283A>G of SCN2A gene is the novel mutation	Epileptic encephalopathies are severe forms of infantile-onset epilepsy often complicated by severe neurodevelopmental impairments. Some forms of early-onset epileptic encephalopathy (EOEE) have been associated with variants in SCN2A, which encodes the brain voltage-gated sodium channel NaV1	[24]
GABRA1 (gamma-aminobutyric acid type A receptor subunit alpha1)	5q34	Encodes for the voltage-gated sodium channel, neuronal type II, alpha subunit	Ala322Asp or A322D. GABRA1 gene mutation leads to the formation of an abnormal α1 subunit that reduces $GABA_A$ receptor function	*GABRA1* variants have been associated with severe phenotypes such as Dravet Syndrome and early-onset EEs, as well as with variable degrees of developmental delay, behavioral problems, and autistic features	[25]
TBC1D24 (TBC1 domain family member 24)	16p13.3	TBC1D24 gene encodes a member of the Tre2-Bub2-Cdc16 (TBC) domain-containing RAB-specific GTPase-activating proteins, which coordinate Rab proteins and other GTPases for the proper transport of intracellular vesicles	Mutations in Tre2-Bub2-Cdc16 (TBC) domain family member 24 genes are associated	TBC1D24-related epilepsy syndromes show marked phenotypic pleiotropy, with multisystem involvement and severity spectrum ranging from isolated deafness	[26]
KCNT1 (potassium sodium-activated channel subfamily T member 1)	9q34.3	Encodes a sodium-activated potassium channel	KCNT1 gene mutations involved in MMPSI change single-protein building blocks (amino acids) in the KCNT1 protein	KCNT1-related frontal lobe epilepsy has some degree of developmental delay or cognitive impairment, but typically they are able to walk and talk. Many people with related frontal lobe epilepsy may also have psychiatric or behavioral problems such as depression, anxiety, or ADHD	[27]
CPA6 (carboxypeptidase A6)	8q13.2	Encodes a member of the peptidase M14 family of metallo-carboxypeptidases	CPA6 mutations in patients with juvenile myoclonic epilepsy and identified two novel missense mutations: Arg36His and Asn271Ser	Epilepsy patients with mutations in CPA6 have been reported with brain malformations, intellectual disability, and hippocampal sclerosis	[27]
EFHC1 (EF-hand domain-containing protein 1)	6p12.2	Encodes an EF-hand-containing calcium binding protein Encoded protein likely plays a role in calcium homeostasis	F229L mutation causes alteration in EFHC1 gene	Mutant EFHC1 expression disrupts radial and tangential migration by affecting the morphology of radial glial and migrating neurons, therefore, disrupts brain development	[28]

Table 2 Common genes involved in migraine

Gene	Location	Function	Mutation	Impairment	Reference
KCNK18 (potassium channel subfamily K member 18)	10q25.3	Encodes TWIK-related spinal cord potassium channel (TRESK) or $K_{2P}18.1$	Mutation in the KCNK18 gene that interrupts TRESK function. Involve p.Trp101Arg (W101R) missense mutation in KCNK18 gene	Frameshift mutation in TRESK potassium channel but has dominant negative effect due to alternatively translated TRESK fragment which downregulates TREK1 and TREK2 potassium channels	[29]
CSNK1D (casein kinase 1 delta)	17q25.3	Encodes an enzyme CKI-delta or CK1δ	S97 mutation, casein kinase 1 isoform delta is mutated (involve tau protein)	Loss-of-function (partial). Casein kinase Iδ phosphorylates mammalian clock protein PER2. CKIδ also phosphorylates and regulates GJA1/Connexin43, an astrocytic gap junction protein and migraine GWAS loci	[30]
ALPK1 (alpha-protein kinase 1)	4q25	ALPK1 gene encodes an alpha kinase	Cause mutations in ALPK1 gene (involve in ROSAH syndrome)	Possible gain-of-function. May affect ciliary formation, regulation of apical transport. Etiology of migraine unclear, but kinase function may affect CGRP activity	[30]
PNKD (Paroxysmal non-kinesigenic dyskinesia)	2q35	Encodes glucose transporter	Heterozygous mutation of c.1022delC; p.P341fs*2 was identified in the *PNKD*	Missense mutations affect protein cleavage and stability. PNKD interacts with synaptic active zone proteins, and mutant protein is less effective at inhibiting exocytosis, resulting in ↑ neurotransmitter release	[30]
SLC1A3 (solute carrier family 1 member 3)	5q13.2	Encodes glial glutamate transporter	Cys186Ser and Trp387Pro variants are involved	Spectrum of FHM3 mutations is highly complex; biological mechanisms remain unclear; however, mutations result in a ↓ in inhibitory transmission which triggers a ↑ in excitatory transmission	[30]

affect the neurotransmitter release and dysregulation of neuronal excitability involved in migraine, benign familial infantile seizures, and paroxysmal kinesigenic dyskinesia [46].

Genetically determined dysfunction of these ion channels and the associated proteins cause changes in neuronal ion concentration, leading to cortical excitability. Imbalance between inhibitory and excitatory factors has been hypothesized to play a key role in epilepsy as well as migraine (Fig. 1) [18]. One of the clear genetic contributions to epilepsy and migraine is SCN1A gene, located on chromosome 2 that encodes for the α-1 subunit of the voltage-gated sodium channels. Sodium channels are mostly located in the cerebral cortex and spinal cord that is closely related to the regulation of action potential. SCN1A gene mutations have been reported to result in seizures and occurrence of FHM3. Mutations in this gene have been commonly observed in epileptic patients [37, 47]. The Dravet syndrome (DS) and infant idiopathic comprehensive seizures and generalized seizures with febrile seizures plus (GEFSþ) and partial seizures with febrile seizures plus (PEFSþ) have been reported to be associated with mutations in this gene [48]. With about 650 heterozygous SCN1A mutations, an average mutation rate of about 85% in DS patients has been observed [49, 50]. About half of these mutations were missense, and half were nonsense. These either increase or decrease the sodium channel function. SCN1A mutations have also been reported to be associated with FHM3 [51]. Some mutations including Q1489K, L1649Q, I1498M, F1661L, and L1624P caused FHM3 but not seizures [12, 37, 52, 53]. However, mutations like L263Q, T1174S, Q1489H, and L263V were found to be associated with both FHM and epilepsy [54, 55]. Out of these Q1489H and F1499L were also associated with elicited repetitive daily blindness (ERDB) [56, 57]. Different types of SCN1A mutations affect the functioning of channels in various ways (Fig. 2). The Q1489K and L1649Q mutations lead to pure FHM3 inhibiting neuronal function, especially the GABA intermediate neurons [58, 59]. On contrary, some studies involving members of Portuguese family bearing L263V mutation in FHM had complex partial seizures or generalized seizures [50, 58, 59]. The L263V alteration leads to the enhancement of channel function responsible for recovery of sodium channel inactivation, thereby prolonging the duration of action and increasing the neuronal excitability. Therefore, this gene variant may lead to epilepsy and FHM in the same individual [60]. CACNA1A gene present on chromosome number 19 encodes the α-1 subunit of the voltage-dependent P/Q calcium channel. The P/Q calcium channel regulates the release of glutamate and serotonin by increasing the flow of calcium to stimulate the presynaptic membrane. CACNA1A gene alterations may impair calcium channel

Table 3 Common genes involved in migraine and epilepsy

Gene	Location of gene	Role of gene	Encoded protein function	Mutation	Impairment	Reference
CACNA1A (calcium voltage-gated channel subunit alpha1 A)	Locus 19p13, between microsatellite markers D19S216 and D19S215	*CACNA1A* gene encodes for the Ca2.1α1 subunit	Voltage-gated P/Q-type calcium channels. P/Q-type calcium channel mediates neuro-transmitter release by promoting the flow of calcium to stimulate the pre-synaptic membrane	Mutations are often near the ion channel or in the voltage sensor. Most common mutation is T666M. Genetic mutations can damage Cav2.1 channel function	*CACNA1A* gene mutations may be shared between patients with absence seizures and patients with FHM. Impair the function of cortical GABA neurotransmitter	[31–34]
ATP1A2 (ATPase Na+/K+ transporting subunit alpha 2)	1q23	Codes for the α2 subunit of Na^+/K^+ ATPase	Na^+/K^+ ATPase. This can regulate the extracellular K^+ concentration	M721T and R689Q mutations of the *ATP1A2* gene were found in FHM2. D718N and P979L mutations increase the risk for epilepsy	Na^+/K^+ ATPase function is impaired. Abnormal Na^+/K^+ ATPase system function disrupts the K^+ gradient and impairs glutamate clearance, which likely contributes to CSD, FHM, and epilepsy	[34–36]
SCN1A (sodium voltage-gated channel alpha subunit 1)	2(2q24.3)	*SCN1A* gene encodes for Nav1.1—a voltage-gated sodium channel	Voltage-gated sodium channel α subunits	Q1489K and L1649Q mutations cause FHM3. L263V mutations can result in epileptic seizures	Different types of *SCN1A* mutations result in different effects on channel function. Mutation of the *SCN1A* gene can result in seizures and FHM3	[34, 37, 38]
PRRT2 (proline-rich trans-membrane protein 2 gene)	16p11.2	Encodes a 340-amino acid trans-membrane protein	Voltage-dependent sodium channels	Mutations occur in the second and third exons of the *PRRT2* gene. c.6 49dupC is a hotspot for *PRRT2* mutation	Mutation causes an error in the DNA replication process that results in a truncated *PRRT2* protein with only 217 amino acids. *PRRT2* mutation impairs SNAP25 function, which then changes CaV2.1 activity, causes neuronal hyperexcitability, and results in epilepsy and hemiplegic migraine	[34, 39–41]

function, causing generalized epilepsy [61]. CACNA1A gene mutations may occur either in epileptics or FHM. However, at the same time CACNA1A mutations may also lead to FHM1 by affecting CSD, a study on mutant mice (R192Q) showed imbalance in excitation and inhibition of calcium channel in cortical neurons, thereby reducing the threshold for CSD and accelerating its propagation [23]. Another study showed that S218L mutant mice are highly sensitive to CSD [24]. ATP1A2 present on chromosome 1 encodes α-2 subunit of Na+/K+ ATPase. Alpha2 subunit has been reported to be expressed in neurons and astrocytes. Na+/K+ ATPase controls the K+ extracellular

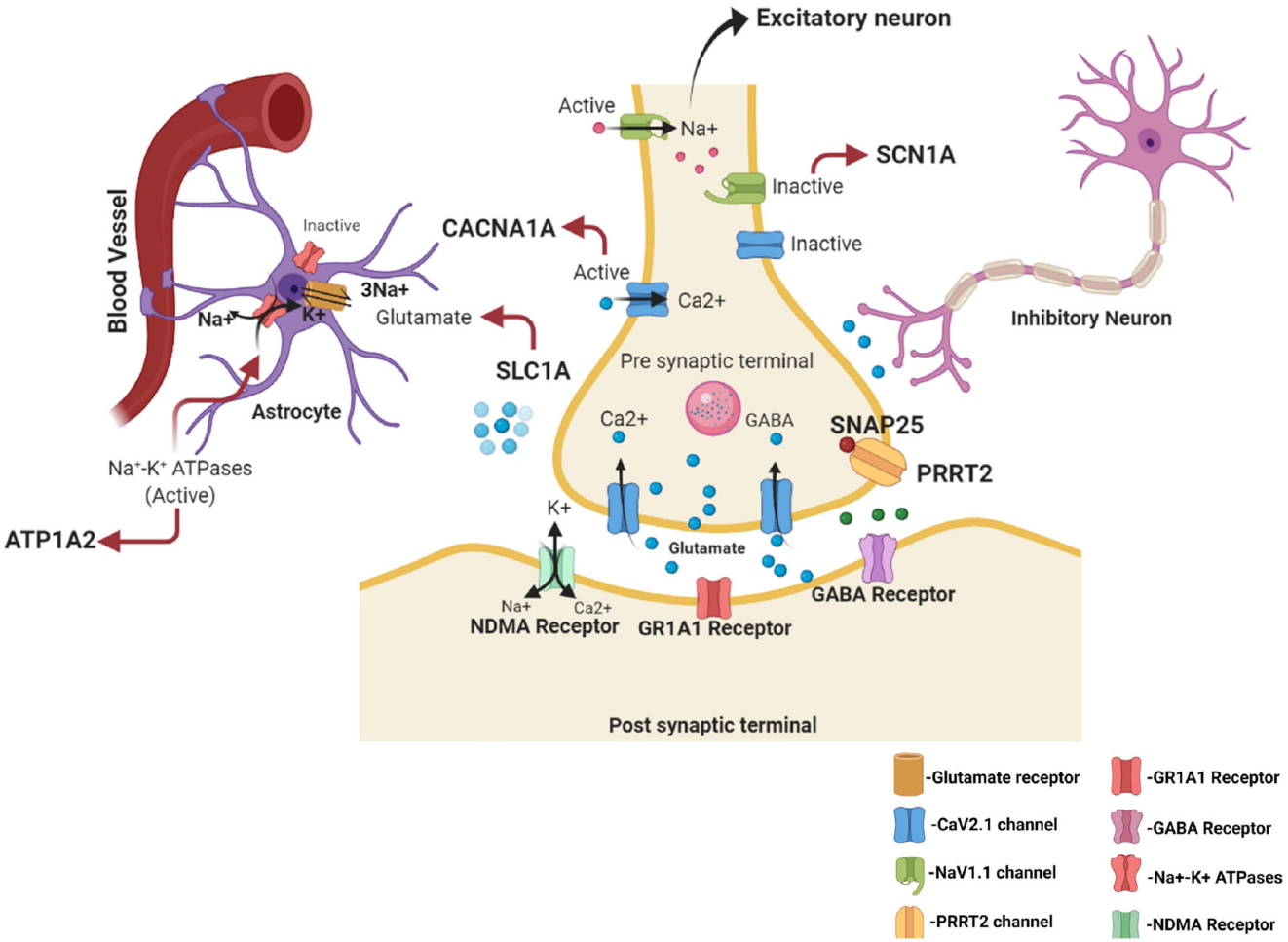

Fig. 2 Schematic representation of a tripartite synapse and the proteins encoded by the different genes involved in migraine and epilepsy: (a) CACN1A gene, encodes for the pore-forming α_{1A}-subunit ($Ca_V2.1$) of P/Q-type calcium channels. Alterations in CACN1A gene lead to the alteration in important functional region of $Ca_V2.1$ channel especially as pore lining. Changes in biophysical properties of channel lead to greater Ca^{2+} influx, mainly due to the hyperpolarizing shifts. Gain of function of excitatory neurotransmission leads to increase synaptic strength mainly due to increased action potential-evoked Ca^{2+} influx via altered P/Q calcium channels. (b) ATP1A2 gene, encodes $\alpha 2$ isoform of the main catalytic subunit of Na^+-K^+ transporter (here, Na^+-K^+-ATPase). This $\alpha 2$ isoform is mainly expressed in astrocytes. The role of Na^+-K^+-ATPase is to maintain the resting potential. Na^+-K^+ transporter. Here Na^+ gradient maintained by Na^+-K^+ transporter is required by astrocytes for the clearance of extracellular glutamate. Glutamate uptake is mediated by the glutamate receptors, i.e., GLAST AND GLT-1 encoded by EAAT1 and EAAT2 genes, respectively. Glutamate uptake is driven by the efflux of three Na^+ ions. Altered Na^+-K^+ transporter reduces the ability of astrocyte to remove K^+ ions that accumulates extracellularly during the action potential, thereby promoting therefore promote neuronal hyperexcitability and indirectly CSD. (c) SCN1A gene, encodes for pore-forming $\alpha 1$-subunit of neuronal type I voltage-gated sodium channel $Na_v1.1$. Alterations in this gene cause biophysical changes in Na^+ transport like abnormal regulation of the gate. Loss of function mutations in $Na_V1.1$ cause impaired functioning of GABAergic inhibitory neurons, resulting in disturbed neuronal synchronization. Gain of function mutations in $Na_V1.1$ lead to excessive excitability of glutamatergic neurons. As the action potential arrives at the nerve terminal, GABA present in the vesicles gets releases, under the action of Ca^{2+} influx. Gain of function or loss of function mutations in SCN1A gene cause neuronal hyperexcitability by disturbing the synthesis of GABA from glutamate and further by hampering its binding to GABA receptor.

concentration in astrocytes, and increased K+ concentration is associated with CSD. This enhances the excitability of neurons and results in a threshold triggering CSD. Abnormal function of Na+/K+ ATPase system on account of ATP1A2 gene mutations results in destruction of K+ gradient thereby influencing glutamate clearance, which may cause seizures, CSD, and FHM. Mutations in ATP1A2 have also been found to cause epilepsy [25].

Treatment Strategies and Future Directions

Migraine and epilepsy have a major socioeconomic impact on patients and their families. Most of the anti-epileptic drugs (AEDs) are prescribed to migraine patients, because of the same pathophysiological mechanisms shared by epilepsy and migraine. It is very crucial to understand the rationale for AEDs in prevention and treatment of migraine, in order to determine the clinical care precisely. As we know, epilepsy

and migraine show a twofold average risk for comorbidity [22]. This endorses the use of AEDs in the treatment of both the disorders. However, the mechanisms of these drugs are not clearly understood as far as their use in treatment of migraine is concerned. It is believed that AEDs block excitation of the neurons (by controlling ion channels) and thereby CSD that might be a key player in the development of migraine. Various clinical trial studies have demonstrated that the use of AEDs in treatment of migraine is well known and effective [26, 27]. Although there are only few AEDs like valproate and topiramate which are currently being used as first-line agents in treatment of migraine, many other drugs like zonisamide, acetazolamide, lamotrigine, and oxcarbazepine are under considerations, although not as first-line treatment [22, 28]. The exact mechanism of valproate is not clearly understood in migraine, but it actually increases the GABA levels in brain by activating glutamic acid decarboxylase enzyme and via inhibition of GABA-degradative enzymes. On the other hand, it also inhibits the voltage-gated ion channels (T-type) by targeting SCN1A and CACNA1A genes and thereby reduces the effect of inflammation of neurons in the brainstem (central trigeminal nerve) [29]. Topiramate modifies the nerve excitability by blocking voltage-gated sodium channels (via targeting SCNA1A gene) and L-type voltage-activated calcium channels. It also enhances the inhibitory effect of GABA by blocking carbonic anhydrase activity [30]. Another drug lamotrigine acts as antagonist to high-voltage-activated n-, P-, and Q-type channels encoded by SCN1A and CACNA1A genes [31]. In spite of the good efficacy of these drugs, some patients do not get required effect of these drugs on account of ADRs. So, the adverse effects, compliance, and cost of prolonged treatment are important issues because they are discovered coincidently without taking into account the pathophysiology of the migraine. Both epilepsy and migraine are multifactorial disorder with a genetic component and environmental factors interacting with genome. However, the genetic contribution to epilepsy is well understood, and the pharmacogenetic studies have been identified the alterations in genes responsible for variations in inter-individuals response to AEDs as well as ADRs. More studies are needed to delineate the roles of newer and existing AEDs in migraine prevention. Targeting the shared genes by both the diseases might be helpful in generating new and effective treatments for these comorbid diseases. Three significant genes CACNA1A, SCN1A, and ATP1A2 have been found to be common in pathogenesis of both the disorders. However, there are certain concerns that have been highlighted by Cestele et al. (2013) regarding the T1174S variant of SCN1A gene which was observed to induce two contrasting effects: a loss of function that was caused by modification of activation properties and a gain of function that was reported to be caused by increased persistent current. The later was not intrinsic property of the mutation but, on the contrary, was generated by a modulation. Mutation analysis was carried out by sequencing of the gene whereas functional analysis was carried out by expressing the mutant allele in tsA-201 cells. The switch between gain of function and loss of function was understood using a computational model [32]. Therefore, the modulations might switch the effect of a particular variant from epileptogenic to promigraine. There seem to be complex genotypic-phenotypic relationship of SCN1A mutations. This aspect needs to be expressed for other significant genes contributing to both the disorders. Therefore, if new drug molecules are designed to regulate the expression of these genes, the modulations that might be responsible for phenotypic switch have to be taken into consideration. If no such modulations are observed in other genes, then the novel drug molecules can be designed accordingly. In addition current high-throughput genetic technologies like CRISPR-Cas9 can also be explored in this direction [33, 34]. For example, a study carried out to generate a disease model to explore the pathophysiological mechanisms in epilepsy is caused by *SCN1A* loss-of-function mutation using CRISPR/Cas9 genome-editing technology [35]. Further, the available data based on transcriptomic profiling addresses miRNAs as treatment strategies, and their status in clinical trials is highly promising. Various transcriptomic-based studies have been carried out to delineate the disease pathophysiology and new possibilities for the identification of molecular targets for future pharmacological strategies in the treatment of these comorbidities [36, 38–41, 62]. Further proteome and metabolome analysis can also be carried out to understand the common pathophysiological mechanisms shared by epilepsy and migraine.

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Author Contribution Prof Anjana Munshi and Prof Gagandeep Singh contributed to the conception and design of the study. Ms. Palvi Gotra and Ms. Nidhi Bhardwaj performed the literature survey and helped in writing the manuscript along with Mr. Abhilash Ludhiadch. Both Ms. Palvi Gotra and Ms. Nidhi Bhardwaj also helped in drawing the figures. Mr. Abhilash Ludhiadch compiled the study and edited the manuscript

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