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Title
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Permalink
https://escholarship.org/uc/item/2qs729sd

Journal
Annual review of physiology, 77(1)

ISSN
0066-4278

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Publication Date
2015

DOI
10.1146/annurev-physiol-021014-071814

Peer reviewed

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Annu. Rev. Physiol. 2015.77:525-541. Downloaded from www.annualreviews.org
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Episodic and Electrical Nervous System Disorders Caused by Nonchannel Genes

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Annu. Rev. Physiol. 2015. 77:525–41

First published online as a Review in Advance on October 17, 2014

The *Annual Review of Physiology* is online at physiol.annualreviews.org

This article's doi:
10.1146/annurev-physiol-021014-071814

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Keywords

channelopathies, migraine, epilepsy, familial disorders, nonchannel causes of electrical diseases

Abstract

As noted in the separate introduction to this special topic section, episodic and electrical disorders can appear quite different clinically and yet share many overlapping features, including attack precipitants, therapeutic responses, natural history, and the types of genes that cause many of the genetic forms (i.e., ion channel genes). Thus, as we mapped and attempted to clone genes causing other episodic disorders, ion channels were always outstanding candidates when they mapped to the critical region of linkage in such a family. However, some of these disorders do not result from mutations in channels. This realization has opened up large and exciting new areas for the pathogenesis of these disorders. In some cases, the mutations occur in genes of unknown function or without understanding of molecular pathogenesis. Recently, emerging insights into a fascinating group of episodic movement disorders, the paroxysmal dyskinesias, and study of the causative genes and proteins are leading to the emerging concept of episodic electric disorders resulting from synaptic dysfunction. Much work remains to be done, but the field is evolving rapidly. As it does, we have come to realize that the molecular pathogenesis of electrical and episodic disorders is more complex than a scenario in which such disorders are simply due to mutations in the primary determinants of membrane excitability (channels).

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INTRODUCTION

Paroxysmal dyskinesias are a heterogeneous group of disorders characterized by sudden transient attacks of recurrent brief episodes of abnormal hyperkinetic involuntary movements on a spectrum from dystonia (sustained contractions) and athetosis (writhing) to chorea (small, dancelike movements) (1, 2). Paroxysmal dyskinesias can be subclassified, on the basis of duration of episodes and precipitating factors, into kinesigenic [paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC), formerly reported as ICCA syndrome; MIM 602066, OMIM 128200], nonkinesigenic [paroxysmal nonkinesigenic dyskinesia (PNKD); OMIM 118800], and exercise induced [paroxysmal exercise-induced dyskinesia (PED); OMIM 612126] (1). As with other episodic disorders, stress lowers the threshold for having attacks. All show autosomal-dominant inheritance with high penetrance, as well as early onset ranging from infancy to childhood. Myoclonus is another episodic hyperkinetic disorder manifesting as involuntary jerking movements caused by contractions of a muscle or group of muscles. Anatomically, myoclonus can arise in the cortex, brain stem, or spinal cord. This article focuses on recent developments in the field of paroxysmal dyskinesia and reviews an assortment of other episodic and electrical disorders (such as audiogenic epilepsy and myoclonus) in which the causative genes do not encode channels.

Paroxysmal kinesigenic dyskinesia (PKD) was first described in 1967 (3). PKD is the most common type of paroxysmal dyskinesia and has an estimated prevalence of 1 in 100,000 individuals (4, 5). PKD patients share common phenotypic features characterized by very brief (seconds to <1 min) but frequent (up to hundreds of times per day) attacks of dystonic or choreiform movements precipitated by startle or sudden voluntary movements (4). Attacks tend toward the choreoathetotic end of the dyskinesia spectrum. The syndrome of PKD/IC typically presents in the first year of life with benign, afebrile infantile convulsions that spontaneously resolve by 2 years of age. Then, in childhood, these individuals begin to have PKD (4, 6). The attacks in PKD are quite remarkable in that they are precipitated by sudden movement (i.e., a movement-induced disorder). Some patients report that they can induce attacks by simply thinking about making a movement. There are often sensations of impending attacks (so-called auras) consisting of numbness or paresthesias in the affected body parts. Patients with PKD/IC have preserved consciousness between attacks and respond well to antiepileptic drugs (AEDs) such as carbamazepine and phenytoin (4, 6).

PNKD was first described in 1940 (7). Symptoms of PNKD typically include dystonic and choreatic involuntary movements that last from minutes to several hours. In PNKD, attacks tend toward the dystonic end of the dyskinesia spectrum. Unlike the case of PKD, voluntary movements do not trigger a PNKD attack. Rather, attacks are precipitated by other factors such as alcohol, caffeine, sodas, tobacco, emotional stress, fatigue, and hunger. PNKD patients often have premonitory sensations preceding attacks. Patients with PNKD also remain conscious between episodes, but unlike the case of PKD patients, PNKD patients' symptoms do not clinically respond well to many AEDs. Clonazepam and diazepam are the most effective medications for PNKD patients (8).

PED was first described by Lance (9) in 1977. PED is a rare form of paroxysmal dyskinesia that can occur in isolation or in association with epilepsy (10–12). PED is characterized by combined chorea, athetosis, and dystonia induced mainly by prolonged exercise, and episodes last between 5 min and 2 h (10, 11, 13). The PED attacks are typically restricted to the exercised limbs (12). PED is accompanied by reduced cerebrospinal fluid glucose levels, and often with other disease manifestations such as epilepsy, mild developmental delay, and hemolytic anemia (11, 12). Compared with treatment of PKD and PNKD, treatment of PED is difficult, although some beneficial effects are reported by using AEDs (10, 13). Interestingly, application of ketogenic diet to PED patients generally results in marked improvements in symptoms (10–12, 14).

EPISODIC DISORDERS CAUSED BY NONCHANNEL GENES

Frings Audiogenic Epilepsy: Mass1 (Gpr98)

The *Frings* mouse, a strain harboring a spontaneous mutation on the Swiss albino background, is one of many mouse and rat strains that are susceptible to audiogenic seizures. The *Frings* mouse seizure phenotype is characterized by wild running, loss of righting reflex, tonic flexion, and tonic extension in response to high-intensity sound stimulation. This phenotype shows an autosomal-recessive transmission pattern. By genetic mapping and linkage analysis of *Frings* mice, the seizure gene locus named *mass1* (monogenic audiogenic seizure susceptible) was localized to an approximately 3.6-cM interval in the middle of mouse chromosome 13 (15). Subsequently, through the use of fine mapping, physical mapping, and candidate gene sequencing of the *mass1* locus, a mutation in a novel gene, *Mass1* [also termed G protein–coupled receptor 98 (*Gpr98*)], was identified and shown to be responsible for the *Frings* phenotype. The mutant allele harbors a single-base-pair deletion (c7009delG) leading to premature termination (V2250X) of the encoded protein (16). Testing the auditory brain stem response of *Frings* mice demonstrated that mice possessing the *Frings Mass1* allele exhibit a mild to moderate level of hearing impairment that is present from the days following hearing onset (17). Interestingly, the BUB/BnJ mouse, another mouse strain with audiogenic seizure susceptibility, also has the same *Mass1* mutation as the *Frings* mouse (16). In the BUB/BnJ strain, the *Frings Mass1* allele is accompanied by a homozygous, strain-specific 753G-to-A mutation of the cadherin 23 gene ($Cdh23^{ahl}$); BUB/BnJ mice exhibit early impaired hearing at 3 weeks of age, and they become deaf at 20 weeks of age (16, 19). Thus, in contrast to the lifelong seizure susceptibility seen in *Frings* mice, BUB/BnJ mice lose seizure susceptibility at approximately 3–5 weeks of age as hearing function deteriorates (16, 19).

The human ortholog of the *Mass1* gene resides on chromosome 5q14. Interestingly, investigators reported that a familial form of febrile seizure (FEB4; OMIM 604352) also mapped to this region of chromosome 5 (20). Subsequently, DNA samples from multiple families with febrile seizure linked to chromosome 5q14 were sequenced for identifying mutations in the human *MASS1* gene. No mutations were found in the coding region of *MASS1*, except that one FEB4 family was identified as harboring a nonsense mutation (S2652X) causing a deletion of the C-terminal 126-amino-acid residue (21, 22). These results suggested that mutation in *MASS1* may be associated with the seizure phenotype but does not contribute to most cases of febrile seizures.

Recently, the *MASS1* gene was identified to associate with Usher syndrome type IIC (USH2C). Usher syndromes, which can be divided into three clinical subtypes (USH1, USH2, and USH3), are clinically and genetically heterogeneous autosomal-recessive disorders characterized by sensorineural hearing deficiencies at birth and by the later development of progressive retinitis pigmentosa (RP) (23, 24). USH2, the most common form of the Usher syndrome, presents a moderate to severe sensorineural hearing loss that is stable in most cases with normal vestibular function and RP. Multiple USH2 families have been tested for mutations of the *MASS1* gene, and several dozen pathogenic mutations in *MASS1*, which is responsible for USH2, have been identified. Such mutations include frame shift mutations; nonsense mutations; splice mutations; missense mutations; and homozygous, large-deletion mutations (25–31). Most mutations reported in the *MASS1* gene are nonsense mutations and frame shifts located either in the large N-terminal ectodomain or in the C-terminal region, and such mutations result in dramatically truncated proteins (25). Intriguingly, in one USH2 digenic case, a heterozygous frame shift mutation in the *MASS1* gene, and a heterozygous frame shift mutation in the PDZ domain–containing 7 (*PDZD7*) gene, was identified (32), implying possible interactions between MASS1 and PDZD7 in pathophysiological pathways of USH2.

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At least three different isoforms of MASS1/Mass1 have been identified in the human and mouse (16, 31, 33). The full-length mouse *Mass1* cDNA spans 19,329 bp and encodes a protein of 6,298 amino acids, whereas the corresponding human *MASS1* cDNA has 19,320 bp and encodes a protein of 6,307 amino acids (33). The *MASS1* gene contains 90 exons and extends over 600 kb within the genome. The biggest isoform of MASS1, possibly the largest cell surface protein, is a 700-kDa orphan G protein–coupled receptor having several known domains, including 35 CalX-β domains, 1 LamG/TspN/PTX homology domain, 7 EAR (epilepsy-associated repeat) regions forming a putative β-propeller folding domain, a GPS proteolytic site, a B-family seven-transmembrane (TM) domain, a putative intracellular tail with multiple potential serine phosphorylation sites, and a putative PDZ-binding C-terminal end (33, 34). The CalX-β module is a Ca^{2+}-binding regulatory region and shares homology with two such motifs in the large intracellular regulatory domain of Na^{+}/Ca^{2+} exchangers. The presence of dozens of CalX-β domains in the extracellular N terminus of MASS1 suggests that Ca^{2+} may be an important regulator of MASS1 and that MASS1 may be an extracellular Ca^{2+} sink, may be an extracellular Ca^{2+} monitor sensitive to the regulation of intra- and extracellular Ca^{2+} trafficking, or may be involved in Ca^{2+}-dependent cell adhesion (33, 34). The EAR region of MASS1 shares homology with the extracellular C terminus of the leucine-rich, glioma-inactivated 1 gene (*LGI1*) (34), which is responsible for autosomal-dominant partial epilepsy with auditory features (OMIM 600512), a rare form of idiopathic lateral temporal lobe epilepsy characterized by partial seizures with auditory disturbances (35, 36). The EAR domains may play an important role in the pathogenesis of epilepsy, possibly through protein-protein interactions having antiepileptic effects or by being involved in axon guidance or synaptogenesis (34).

In situ hybridization studies with mouse embryo sections indicated that high-level expression of *Mass1* RNA was restricted to the developing central nervous system (CNS) and eye. High expression of *Mass1* RNA in the ventricular zone, the origin of neural progenitor cells during embryonic neurogenesis, suggested an important role for Mass1 in CNS development (33).

Mass1 knockout mice lacking exons 2–4 of *Mass1* showed no obvious histological abnormalities in their brains but were susceptible to audiogenic seizures (37). In another *Mass1* knockout mouse model, in which the TM domain and C terminus of *Mass1* (Vlgr/del7TM) were deleted, the homologous knockout mice were susceptible to audiogenic seizures, similar to the case of *Frings* mice (38). These results suggest that both the extracellular N terminus containing CalX-β domains and C-terminal TM/cytoplasmic domains are critical for normal neuronal functions of Mass1. Loss of these important functional domains of Mass1 underlies the seizure phenotypes in both mutant mouse strains, possibly because signals that regulate the early stages of neural development are disrupted. Mass1 is a component of the ankle link complex and is transiently expressed during hair bundle development (39, 40). Homozygous Vlgr/del7TM mutant mice showed pathogenic phenotypes of hair bundle development such as absent ankle links in cochlea hair cells, disorganized hair bundles observed after birth, impaired mechanotransduction in cochlear hair cells, loss of hair cells from the basal half of the cochlea in 2-month-old mice, and severe deafness by 3 weeks of age (38). These results indicate that Mass1 is required for the formation of the ankle link complex and for the normal development of cochlear hair bundles. The Vlgr/del7TM mutant mice exhibit an auditory phenotype similar to that observed in patients with USH2 (38).

Several mouse strains with Mass1 deficiency show seizure phenotypes, but the detailed mechanisms connecting Mass1 functions and seizure phenotypes are still largely unknown. Immunohistochemical staining revealed that Mass1 shows enriched expression in myelin-forming oligodendrocytes. The Mass1 protein is also highly enriched in the superior and inferior colliculi; both regions are critical areas for the initiation and propagation of audiogenic seizures (41). MASS1 helps control the expression of myelin-associated glycoprotein (MAG) by regulating

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the stability of MAG though inhibiting MAG ubiquitylation. In *Frings* mice, Mag expression is dramatically decreased (41). MASS1 interacts with Gα s/Gα q and activated PKA and PKCδ/θ in response to extracellular Ca^{2+} in vitro (41). Taken together, these data suggest that MASS1 may be involved in sensing extracellular Ca^{2+} and in activating cytosolic PKA/PKC pathways to regulate myelination by means of MAG protein stability in myelin-forming oligodendrocytes of the auditory pathway. Deficiencies in normal MASS1 expression may cause damage to myelin of the auditory pathway and in turn greatly reduce the threshold for induction of audiogenic seizure. Further work is required to determine whether MASS1 is involved in regulating other pathways, and these studies may provide insights into novel intracellular signaling pathways in epilepsy and novel targets for developing anticonvulsants.

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Familial Cortical Myoclonus and the Role of NOL3

Myoclonus is characterized by sudden, brief involuntary movements and can be severely debilitating. Myoclonus is thought to arise from spinal, subcortical, or cortical neuronal hyperexcitability, and electrophysiological examination can readily distinguish among these foci of aberrant excitation, but little is known about the mechanisms of hyperexcitability (42).

Myoclonus is sometimes seen in association with epilepsy, but in two Mendelian movement disorders, seizures do not occur. The first, myoclonus-dystonia syndrome (also termed DYT11; OMIM 159900), is characterized by juvenile-onset myoclonus and/or dystonia that is caused by autosomal-dominant mutations in the ε-sarcoglycan gene (*SGCE*) (43, 44). The second myoclonic disorder, termed familial cortical myoclonus (FCM; OMIM 614937), was recently described (45).

The FCM family is a large, four-generation Canadian Mennonite family in which 11 individuals had adult-onset, slowly progressive cortical myoclonus variably affecting the face and upper and lower extremities. FCM patients showed an adult-onset pattern ranging from the second to the seventh decade, and myoclonus became progressively more frequent and widespread over decades (45). The pattern of inheritance was autosomal dominant. Myoclonus was triggered by action, by sudden movements, and/or by inadvertent somatosensory stimuli, but not by light, noise, or startle. Symptoms were reportedly aggravated by fatigue, exertion, sleep deprivation, emotion, and hunger (45).

By using genome-wide SNP mapping, classic microsatellite linkage analysis, and fine mapping of recombinants in this FCM family, a 5.57-Mb critical region on chromosome 16q containing more than 100 genes was identified. Subsequently, targeted massively parallel sequencing of all known and predicted genes in this critical region was performed, and only one variant predicted to cause an amino acid change was found to completely cosegregate with FCM. This variant is a G-to-C transversion in the nucleolar protein 3 gene (*NOL3*) and predicts an E21Q missense mutation in the NOL3 protein. The variant was not present in any genome database or control samples (45).

NOL3 encodes a 208-amino-acid protein that is expressed in the heart, skeletal muscle, and brain (46–48). The mutated residue, E21, is located in the N-terminal caspase activation recruitment domain (CARD), which is a motif mediating protein-protein binding via electrostatic interactions (49, 50). Several experiments have predicted that the E21Q missense mutation may cause changes in the function of the NOL3 protein. Sequence alignment and comparison showed that in NOL3 homologs (which can be identified only in higher vertebrates), the CARD motifs are extremely conserved, and the E21 residue is 100% conserved (45). In silico homology modeling has predicted that the E21Q mutation, which changes an acidic glutamate residue to a neutral glutamine residue, may alter the electrostatic surface potential of the NOL3 CARD. In the heterologous system, expression of the tagged E21Q mutation yielded two clear NOL3

protein bands, whereas expression of wild-type NOL3 mainly yielded only one band (with a very faint second band observed), suggesting that the mutation alters posttranslational modification of the NOL3 protein in cells (45).

The NOL3 protein interacts with several proteins involved in apoptosis pathways, and NOL3 is a well-characterized inhibitor of apoptosis (47, 51–53). However, the mechanism linking *NOL3* mutations and neuronal hyperexcitability remains entirely unknown. The absence of neuronal hyperexcitability phenotypes in *Nol3*$^{-/-}$ mice and the usual expression pattern of the *NOL3* E21Q mutation in the heterologous system strongly argue against the hypothesis that either a dominant-negative mechanism or haploinsufficiency causes FCM (45). Instead, it seems more plausible that *NOL3* mutation causes FCM by a gain-of-function mechanism. This E21Q mutation may change the original posttranslational modification pattern of NOL3 and/or alter interactions of NOL3 with other proteins. More studies are needed to establish the connections between NOL3 functions and neuronal excitability and, in turn, to provide a better understanding of FCM pathophysiology.

To date, only one large FCM family had been found; members of this family harbored a single missense mutation in the *NOL3* gene. Although studies containing substantial genetic, bioinformatic, and biochemical evidence had suggested that *NOL3* is the gene responsible for FCM, the phenomenon of allelic heterogeneity that is the general gold standard of the Mendelian diseases has not been established for FCM. We cannot rule out the possibility that the E21Q variant in NOL3 is a rare variant that is linked to, but does not itself cause, the disease. Further efforts, such as the identification of more FCM families with *NOL3* mutations and/or functional studies using a *NOL3* mutation knock-in animal model, are needed to provide more solid evidence for the demonstration of genetic and/or pathophysiological connections between NOL3 and FCM. Interestingly, a recent study that reported screening *NOL3* for mutations in 107 myoclonic patients of British origin identified a missense mutation (cG238A, A80T) in one of these patients (54). The A80 amino acid residue resides in the N-terminal CARD domain of the NOL3 protein (49, 50) and is conserved across species (54). Surprisingly, this patient showed a phenotype different from the phenotypes we had previously described. This patient presented with subcortical myoclonus and seizures (54). Because no other family members are available for clinical or genetic analysis, the possible pathogenic role of this A80T variant remains uncertain.

Migraine with Aura in Familial Advanced Sleep Phase: Casein Kinase Iδ

Migraine is a common neurological disorder affecting between 10% and 20% of the population, according to different reports (55–57). The clinical presentation is heterogeneous and includes recurrent headache attacks, associated symptoms of vegetative disturbance, and hypersensitivity of various functional systems of the nervous system. Approximately one-third of migraine patients experience transient neurological symptoms mostly involving the visual system prior to or during a migraine attack, which are known as migraine aura (58, 59). Whether migraine with aura and migraine without aura are distinct or overlapping entities is somewhat contested, but it is not uncommon for patients to experience both forms of migraine (56). In migraine genetics, the linkage approach was successfully applied for familial hemiplegic migraine (FHM)—a rare, autosomal-dominant subtype of migraine with aura that is characterized by a transient hemiparesis during the attack (55, 58, 60)—which led to the identification of three FHM genes: *CACNA1A* (FHM1), encoding the $\alpha 1$ subunit of neuronal Cav2.1 Ca^{2+} channels (61, 62); *ATP1A2* (FHM2), encoding the $\alpha 2$ subunit of Na^{+}/K^{+} ATPase pumps (63, 64); and *SCNA1* (FHM3), encoding the pore-forming $\alpha 1$ subunit of neuronal Nav1.1 Na^{+} channels (65, 66). All these genes encode proteins involved in ion transport in the brain.

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Coincidently, when studying families with a sleep disorder termed familial advanced sleep phase (FASP), we identified a gene that is responsible for FASP and migraine in an autosomal-dominant pattern (67). Two FASP families, in which the affected individuals go to sleep unusually early and also wake very early in the morning compared with normal subjects, have been identified to harbor one of two distinct missense mutations (T44A and H46R) in casein kinase Iδ (*CKIδ*) as causes of FASP (67, 68). Of 11 mutation carriers in these two FASP families, 10 were classified as affected, and 1 was classified as probably affected, by migraine by ICHD-2 (*International Classification of Headache Disorders*, second edition) criteria, strongly arguing against the hypothesis that the association of *CKIδ* alleles with migraine at this high ratio is merely by chance.

Members of the highly conserved and ubiquitously expressed pleiotropic *CKI* gene family play major regulatory roles in many cellular processes, including DNA processing and repair, cell proliferation, cytoskeleton dynamics, vesicular trafficking, apoptosis, cell differentiation, circadian rhythms, and cell signaling (69, 70). All CKI isoforms are highly conserved within their N-terminal kinase domains. The highly related isoforms CKIδ and CKIε show the highest homology, but CKI family members are significantly different in length and primary structure of their regulatory noncatalytic C-terminal domains (70). CKIδ protein sequences across species are extremely conserved, and both residues T44 and H46 located in the N-terminal kinase domain are absolutely conserved (67). In vitro experiments showed that the T44A and H46R mutations resulted in reduced CKIδ activity and in greatly decreased maximum transport velocity (V_{max}), suggesting that the mutations reduced the catalytic rate of phosphor transfer (67). Interestingly, both the T44A and H46R mutant forms of CKIδ showed lesser abilities to phosphorylate CONNEXIN43 (Cx43), a known substrate speculated to be relevant to migraine, compared with wild-type CKIδ (67).

To examine whether mutant CKIδ can cause migraine symptoms in vivo, we tested CKIδ-T44A transgenic mice, which were successfully used as an animal model for studying FASP (68). We tested these mice for susceptibility to the migraine-like phenotypes of cortical spreading depression and peripheral allodynia. CKIδ-T44A transgenic mice were more sensitive to pain induced by injection of nitroglycerin (NTG) and showed increasing activation of neurons in the trigeminal nucleus caudalis, identified by significantly increased Fos-positive nuclei, after application of NTG, which is regarded as a common trigger agent for migraine (67).

CKIδ-T44A transgenic mice were also used to investigate the effects of CKIδ mutation on migraine-related cortical excitability. For migraine with aura, the phenomenon of cortical spreading depression is an associated event. Cortical spreading depression is a slow wave of neuronal and glial depolarization followed by sustained underactivity (55, 57, 71). CKIδ-T44A mice show both a significant reduction in the threshold for evoking cortical spreading depression and an increased number of cortical spreading depression events elicited by continuous stimulation, consistent with the increased cortical excitability that has been observed in patients with migraine. At the same time, the cortical vascular response to cortical spreading depression is altered in CKIδ-T44A mice by an enhanced pattern of cortical spreading depression–associated arterial dilation compared with the pattern seen in their wild-type littermates (67).

Astrocytes from CKIδ-T44A mice presented increased spontaneous and evoked Ca^{2+} signaling compared with Ca^{2+} signaling in wild-type mice. This result suggested that the CKIδ-T44A mutation may alter astrocyte signaling, leading to modified cortical excitability and associated vascular responses. Astrocytes can release extracellular messengers, including ATP and glutamate, through forming undocked connexin channels termed hemichannels (72–74). We speculate that hypophosphorylation of Cx43 may lead to more hemichannels than gap junctions in astrocytes (75), potentially leading to increased release of ATP and glutamate. Phosphorylation has been implicated as an important posttranslational modification in (*a*) the regulation of gap junction

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communication at several stages of the cell cycle and the connexin life cycle, such as trafficking, assembly/disassembly, and degradation, as well as in (*b*) the gating of hemichannels or intact gap junction channels (76–79). The cytosolic C-terminal region of Cx43 appears to be the primary region that becomes phosphorylated, and several protein kinases, including PKC, PKA, and CKI, are important in the phosphorylation and regulation of gap junction assembly (80, 81). CKI interacts with and phosphorylates Cx43 in vitro, initially on serines 325, 328, and/or 330 at the C terminus of Cx43. CKIδ may regulate Cx43 gap junction assembly by directly phosphorylating Cx43 (75). Our data showed that Cx43 is hypophosphorylated by both mutant forms of CKIδ, and this hypophosphorylation was also reported in other pathological conditions (such as the ischemic heart) in which phosphorylation of Cx43 at serine residues 325, 328, and/or 330 influences channel selectivity and regulates the efficiency of gap junction assembly (82). Intriguingly, a conditional knockout mouse model lacking astrocytic Cx43 displayed an accelerated pattern of cortical spreading depression propagation and reduced intercellular coupling in the stratum radiatum of the hippocampal CA1 region, and these mice lacking Cx43 in astrocytes showed enhanced locomotory activity (83). Together, these findings suggest possible astrocytic mechanisms by which CKIδ mutations may induce migraine though posttranslational modification of Cx43 and then indirect regulation of ion channels. CKIδ is an enzyme involved in modulating functions of numerous proteins, some of which may play roles in migraine pathogenesis. Further work is needed to identify CKIδ substrates that are relevant to migraine. These efforts may further elucidate the unknown cellular and molecular signaling mechanisms of migraine and provide new insights into new therapeutic approaches for migraine.

PAROXYSMAL DYSKINESIAS

Paroxysmal Nonkinesigenic Dyskinesia

PNKD is caused by mutations in the PNKD gene (formerly termed myofibrillogenesis regulator 1), which is located on chromosome 2q (84). Approximately 20 PNKD kindreds of different ethnicities and harboring mutations in PNKD have been identified (84–89). Only three point mutations have been detected in PNKD, and all three are located near the N terminus of the protein, implying that the N terminus may play a pivotal role in the protein's function. Most PNKD patients have either an A7V or an A9V mutation, and a third mutation (A33P) was reported in a single family (90). The PNKD gene has at least three alternate splice forms, which encode proteins of 385, 361, and 142 amino acids. The long isoform of PNKD (PNKD-L) is specifically expressed in the CNS, whereas the medium isoform (PNKD-M) and the short isoform (PNKD-S) are ubiquitously expressed. The mutations are harbored in both PNKD-L and PNKD-S (84).

The PNKD gene encodes a novel protein of unknown function, but emerging evidence implies that it may play an important role in synaptic function. First, in heterologous systems, overexpressed PNKD-L is detected at the cell membrane. We showed that it is a membrane-associated protein and not a TM protein. Second, in the CNS, PNKD proteins are exclusively expressed in neurons. Third, PNKD-L was detected in mouse synaptosome extractions and identified in both the pre- and postsynaptic regions of mouse neurons by immunoelectron microscope (84, 91; Y. Shen & L.J. Ptáček, unpublished data). Taken together, the evidence indicates that PNKD is a novel synaptic protein that modulates neuronal activity.

With its synaptic localization, the PNKD protein may participate in regulating exocytosis of neurotransmitters. Some recent experimental results provided evidence for this speculation. PNKD-L interacts with a protein regulating synaptic membrane exocytosis (RIM1/2) both in vitro and in vivo (L.J. Ptáček, unpublished data). RIM proteins are pivotal for synaptic vehicle

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exocytosis because they bind to other important components of the active zone and are involved in all central aspects of neurotransmitter release (92–94). By interacting with RIMs, the PNKD protein can participate in the regulation of exocytosis.

Because the PNKD protein may be involved in neuronal synaptic exocytosis, mutations in the PNKD protein may alter its ability to regulate exocytosis. We have shown that, when coexpressed with RIM1 or RIM2, mutant PNKD-L lost the inhibitory property of controlling exocytosis that is preserved in the wild-type protein in a heterologous expression system (L.J. Ptáček, unpublished data). In primary rat hippocampal neuronal cultures cotransfected with a vesicular pH-sensitive GFP indicator, overexpressed wild-type PNKD significantly reduced neurotransmitter release by 50% compared with neurotransmitter release in controls transfected with an empty vector, but mutant PNKD-L failed to perform this inhibitory function (L.J. Ptáček, unpublished data). These results indicate that mutations of the PNKD protein can interfere with its normal regulation of exocytosis.

For studying the pathophysiology of PNKD, BAC transgenic mice (Pnkd mice) carrying mutations in the mouse *Pnkd* locus equivalent to those found in patients with PNKD were generated, and *Pnkd* wild-type BAC transgenic mice and *Pnkd* knockout mice were also generated for the purpose of comparison. Only mutant *Pnkd* transgenic mice recapitulated the human PNKD phenotype when challenged by caffeine, ethanol, and stress. The Pnkd mice also showed increasing c-fos staining in basal ganglia and elevated dopamine turnover rates in the striatum after induction of PNKD episodes by injection of caffeine or ethanol (91). Such mice also presented nigrostriatal neurotransmission deficits that were manifested by reduced extracellular dopamine levels in the striatum and by a proportional increase in dopamine release in response to caffeine and ethanol challenges. Pharmacological tests of Pnkd mice by application of specific agonists or antagonists of adenosine and dopamine receptors indicated a strong involvement of the striatal indirect pathway in the pathogenesis of PNKD (91). These findings support the hypothesis that the PNKD protein is heavily involved in modulating striatal dopamine release in response to stress and other precipitating factors.

Interestingly, PNKD-L and PNKD-M have a motif homologous to hydroxyacylglutathione hydrolase, which detoxifies methylglyoxal, a compound present in coffee and alcoholic beverages and produced as a by-product of oxidative stress (95–98). Although we have shown that PNKD does not catalyze this reaction (99), PNKD may have enzymatic activity, presumably for some glutathione (GSH) adduct. Indeed, Pnkd mice have lower GSH levels in cortical extracts than do wild-type littermates at rest, implying that PNKD-L may be involved in an enzymatic reaction using reduced GSH as a cofactor (99).

Paroxysmal Kinesigenic Dyskinesia with Infantile Convulsions: The Role of PRRT2

Mutations in the gene encoding proline-rich TM protein 2 (PRRT2), located on chromosome 16p near the centromere, are responsible for PKD/IC (5). Recently, numerous groups identified *PRRT2* mutations in PKD/IC kindreds of different ethnic backgrounds (5, 100–107). In affected PKD families, a remarkable pleiotropy is observed, both between and within families, and patients show a broad spectrum of symptoms such as episodic ataxia, hemiplegic migraine, and benign infantile epilepsy (101, 108–110). More than 60 different mutations have been identified in PRRT2, including coding region mutations (missense, nonsense, frame shift) and splice site mutations. The most common mutation found in PKD patients is the insertion mutation c649_650insC (R217Pfs*8), which occurs in a homopolymer trace of nine cytosine bases that are preceded by four guanines. This sequence structurally has the potential to form a hairpin loop, which may

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cause polymerase slippage and insertion of an additional base during DNA replication (109, 111). Interestingly, this poly-C tract seems to be a hot spot for mutations: In addition to this common insertion mutation, a one-base cytosine deletion (c649delC; R217Efs*12) and a nonsense mutation (cC649T; R217X) were reported in several PKD cases (104, 112–114). *PRRT2* encodes a protein containing 340 amino acid residues with two putative TM domains near the C-terminal end and with a proline-rich region around the middle of the protein (5, 100, 102, 107). The function of PRRT2 is still largely unknown, but our in vitro data make clear that all the mutations result in loss of function (haploinsufficiency). In contrast, for PNKD, the mutations clearly function through a gain-of-function mechanism.

In situ hybridization has revealed that mouse Prrt2 is expressed throughout the brain, with the highest mRNA density in the cerebral cortex (100, 102). Reverse transcriptase PCR experiments also indicated that Prrt2 is expressed both in the brain and in the spinal cord, but not in other tissues. The Prrt2 mRNA concentration in mouse brain is highest on postnatal day 14 and is still expressed at relatively high levels in the adult brain (100). The Prrt2 protein is highly expressed in mouse neuronal tissues (the brain and spinal cord) but is not expressed in other tissues (5). All these findings demonstrate that *PRRT2* encodes a novel protein specifically expressed in neuronal tissues and imply that PRRT2 has a potential role in moderating normal neuronal function. Interestingly, we showed that PRRT2 interacts with synaptosomal-associated protein 25 (SNAP-25) by coimmunoprecipitation performed both in vitro and in vivo (5). SNAP-25, a member of the SNARE protein family, is essential for the transport of vesicles from the Golgi apparatus to the plasma membrane (115). SNAP-25 also participates in forming a complex that is in turn involved in synaptic vesicle membrane docking and fusion (116). SNAP-25 plays a pivotal role in Ca^{2+} -triggered neuronal exocytosis (117, 118). Specifically expressed in neuronal tissues, PRRT2 may play a role in modulating neuronal exocytosis by interacting with SNAP-25.

Although PKD/IC and PNKD are caused by mutations in two different genes, PKD/IC shares dramatic clinical and genetic similarity with PNKD. Both are autosomal-dominant disorders with high penetrance and exhibit a spectrum of episodic hyperkinetic movements ranging from choreoathetosis to dystonia. The dyskinesias typically occur in childhood, worsen through adolescence, and then often improve as patients grow into middle age. Between attacks, patients appear completely normal. Stress can lower the threshold for triggering attacks in both PKD/IC and PNKD (4, 8). These clinical similarities between PKD/IC and PNKD suggest that the disorders may share some degree of similarities at both the molecular and pathophysiological levels.

Coimmunostaining experiments using FLAG-tagged PRRT2 overexpressed in rat primary hippocampal neurons indicated that PRRT2 colocalizes with synapsin-1 at neuronal puncta (5). Synapsin-1 associates with the cytoplasmic surfaces of synaptic vesicles and is also involved in synaptogenesis and in the modulation of neurotransmitter release (119–121). The localization of PRRT2 at neuronal puncta, its colocalization with synapsin-1, and its interaction with SNAP-25 suggest that, just like the PNKD protein, PRRT2 is likely a novel synaptic protein that is located at the presynaptic region and that participates in modulation of neurotransmitter release in response to different stimuli. More work is needed to further test this hypothesis.

Surprisingly, in vitro expression experiments showed that *PRRT2* truncation mutations presented either remarkably reduced or absent expression when transfected alone in the heterologous system. When cotransfected with wild-type PRRT2, PRRT2 protein was present, suggesting that these mutations did not exert a dominant-negative effect on protein levels. Mutant PRRT2 R217Pfs*8, the most common PRRT2 mutation in PKD/IC patients, led to complete abrogation of PRRT2 expression in rat cultured neurons (5). Reduced PRRT2 protein may be caused by nonsense-mediated RNA decay or by accelerated degradation of the mutant protein. These findings are consistent with the idea that PKD/IC mutations are loss-of-function mutations by

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the mechanism of haploinsufficiency. This hypothesis is also supported by several atypical PKD patients with microdeletions of the chromosome 16p region encompassing PRRT2 (122–125).

Paroxysmal Exercise-Induced Dyskinesia: The Role of GLUT1

Mutations in the solute carrier family 2 (facilitated glucose transporter) number 1 gene (*SLC2A1*), located on chromosome 1p, are the cause of PED (126–128). *SLC2A1* encodes the glucose transporter type 1 (GLUT1) protein, which is a 492-amino-acid integral membrane protein with intracellular N and C termini and 12 TM domains. Several mutations, including missense mutations, a frame shift mutation, and a 4-amino-acid deletion that produced additional neurological symptoms, have been identified in the *SLC2A1* gene of PED kindreds (127, 128). A large family formally diagnosed with paroxysmal choreoathetosis with spasticity (129) carries a missense mutation in *SLC2A1* (130). GLUT1 is constitutively expressed in most tissues; is selectively expressed in erythrocytes, brain microvessels, and astroglia; and is the principal glucose transporter in the brain by facilitating glucose across the blood-brain barrier (131, 132).

Kinetic analysis of glucose uptakes in oocytes by injection of cRNA (wild-type or mutant GLUT1) showed that several missense mutations and the 4-base-pair deletion lead to a marked reduction of glucose uptake in vitro. These mutations affect the intrinsic ability of GLUT1 to transport glucose across the cell membrane by markedly decreasing V_{max} but without obviously affecting the Michaelis constant (K_m) and protein stability, trafficking, and insertion into cell membrane (127, 128). These findings support the idea that PED mutations are loss of function and cause haploinsufficiency. We speculate that PED attacks can be triggered by reduced glucose transport when the energy demand after prolonged exercise exceeds available energy supply in specific brain regions such as the basal ganglia (127, 128). But this glucose transporter defect cannot be specific to the basal ganglia because PED patients often suffer other neurological symptoms, including hemiplegic migraine, developmental delay, and epilepsy. Indeed, PED is now regarded as one neurological manifestation of the complex and variable disorder termed GLUT1-deficiency syndrome (GLUT1-DS) (133–135). GLUT1-DS patients show a broad clinical spectrum of symptoms, including infantile seizures, developmental delay, acquired microcephaly, hypotonia, spasticity, complex movement disorders consisting of ataxia and dystonia, and PED with or without epilepsy (136–138). The exact pathophysiological mechanism of PED in GLUT1-DS is not completely clear, and further investigations are essential to gain more insight.

CONCLUDING REMARKS

It is perhaps not surprising that not all heritable episodic and electrical disorders result from mutations in ion channels. However, this field began with cloning of all the genes for the periodic paralyses and nondystrophic myotonic disorders. On the basis of the precedent of ion channel mutations causing these disorders (and subsequently, for example, episodic ataxia, long-QT syndrome, and FHM), many assumed that all episodic disorders would be channelopathies. Although electrical disorders must ultimately be transduced as alterations in membrane excitability, it is now clear that mutations in other kinds of proteins may yield this result. We have therefore proposed a new scheme for classification of these disorders, as outlined in the introduction to this special topic section on episodic and electrical disorders (139).

A growing body of data supports the idea that paroxysmal dyskinesias result from abnormal synaptic (circuit) function as one discrete example of nonchannel disorders. In the case of other disorders like FCM with *NOL3* mutations, *Frings* audiogenic epilepsy with *GPS98* mutations, or

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migraine with *CKI*δ mutations, much work remains to be done to investigate the final pathway to the altered neuronal excitability giving rise to these phenotypes.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This work was supported by grants from the Dystonia Medical Research Foundation, the Bachmann-Strauss Dystonia and Parkinson Foundation, and the Sandler Neurogenetics Fund. L.J.P. is an investigator of the Howard Hughes Medical Institute.

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Physiology

Volume 77, 2015

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