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Combined Neuro-Cardiogenic Epilepsy Syndromes and Novel Mechanistic Insights

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1. Introduction

A large portion of patients with epilepsy without other obvious organ disease die unexpectedly. Epidemiological studies have estimated the rate of unexpected death in patients with epilepsy up to 24 times higher as compared to the general population (Ficker et al., 1998). However, in contrast to a significantly increased risk of sudden death in epilepsy patients, the underlying causes and pathophysiological mechanisms leading to sudden death are not well understood. This important problem is clinically identified as sudden unexplained death in epilepsy (SUDEP). Of note, SUDEP does not include death after prolonged seizures (e.g. status epilepticus) or due to other organ disease which excludes common cardio-pulmonary pathology. SUDEP occurs frequently in patients with idiopathic epilepsy with an estimated prevalence of 2% to 18% (Nashef et al., 2007; Tomson et al., 2008). It has been hypothesized that SUDEP and certain types of seizures may initiate a pathological signal to the heart, which subsequently triggers cardiac dysrhythmias and sudden death in epilepsy (Jehi & Najm, 2008; Surges et al., 2009). Alternatively, dysfunction of fast ion transport mechanisms, which directly control membrane excitability within the context of either the brain or the heart, may directly cause both neuronal or cardiac dysrhythmias. Importantly, if certain genetic defects in ion channel genes coexisted in the brain and heart, this may constitute a candidate mechanism of SUDEP and potentially precipitate life-threatening cardiac dysrhythmias (Nashef et al., 2007). Indeed, recent work has identified ion channelopathies in the context of generalized epilepsy that coexist in the brain and the heart. For the first time, defined molecular mechanisms of coexisting brain and heart dysrhythmias have been shown in genetically engineered rodent models with patient mutations which reproduce both neuronal and cardiac patient phenotypes. This article focuses on previous perspectives and recent insights about molecular epilepsy mechanisms, which underlie both dangerous dysrhythmias in the brain and heart. In addition, novel targeted treatment rationales based on molecular and cellular mechanisms of dysrhythmias are discussed.

2. Can existing genetic epilepsy mechanisms explain unexpected death?

Epilepsy is an episodic dysrhythmia of electrical brain activity in the cerebral cortex marked by abnormal neuronal network synchronization. Approximately 20 genes with major effects on susceptibility to epilepsy have been associated with different seizure syndromes. These epileptogenic genes define distinct as well as common modulatory pathways of neuronal network activity. One group of genetic variants appears to destabilize neuronal signaling through defects which affect the neurophysiology of electrical membrane excitability and synaptic transmission. Another group of genetic variants causes neurodevelopmental effects which perturb the balance between inhibitory and excitatory circuits. Unfortunately, none of the genetically defined epilepsy mechanisms can readily explain molecular pathways which lead to cardiac dysrhythmias as a hypothetical cause of unexpected death in epilepsy.

Due to a high rate of SUDEP in primary epilepsy patients with generalized seizures, it might be important to consider how epilepsy genes are identified and within which pathophysiological context a genetic defect has been further characterized. The following two principal strategies exist: 1) a candidate gene is identified in the context of inherited disorders in patients or animal models and 2) an incidental phenotype identifies a genetic epilepsy syndrome following targeted mutagenesis in animal models. Indeed, both strategies have contributed to a growing list of genes linked to inherited epilepsies. The diversity of distinct phenotypes and their causative gene mutations provides important clues both to a gene's physiological function as well as to a behavioral disease mechanism which might surprisingly reveal overlap with cardiac dysrhythmias. The list of epileptogenic genes spans from intrinsic membrane proteins underlying cell membrane excitability to nuclear transcription factors which control the fate of developing neuronal networks. Accordingly, mechanisms that underlie epilepsy may range from abnormal action potential firing to developmental abnormalities of specific neural circuits. Within the context of unexpected death in epilepsy, mechanisms which directly cause electrical membrane dysfunction and thereby alter fast action potential signaling seem promising to explain either or both brain and heart dysrhythmias. Indeed, recent insight from genetically engineered animal models has uncovered previously unknown epilepsy syndromes and genes in the context of cardiac dysrhythmia syndromes.

2.1.1 Consideration of previous perspectives to explain SUDEP

Risk factors for SUDEP include early onset of epilepsy from age 20 to 40 years, generalized seizures, resistance to anticonvulsant drug therapy, and poor patient compliance (Hitiris et al., 2007). Importantly, several clinical studies have documented abnormalities of the heart rhythm in SUDEP patients suggesting the possibility of co-existing or even synergistic neuro-cardiogenic mechanisms (Britton et al., 2006; Johnson et al., 2009; Nei et al., 2000; Opherk et al., 2002; Zijlmans et al., 2002). Indeed, sudden death caused by dysrhythmia of the heart (in cardiovascular sciences also referred to as *arrhythmia*) represents a frequent cause of electrical organ dysfunction in the general population. The phenotype of cardiac arrhythmia has been linked to a large spectrum of gene variants that include multiple ion channel genes (see 2.1.2). Therefore, a hypothetical mechanism of SUDEP could be that the identical ion channel gene expressed in the brain and the heart becomes dysfunctional due to a mutation, and causes a combined neuro-cardiogenic syndrome including unexpected

death in epilepsy. Is there sufficient evidence for such a combined neuro-cardiogenic mechanism of SUDEP in patients?

In epilepsy patients and also in SUDEP victims a spectrum of cardiac dysrhythmias has been reported including arrhythmias of the atria as well as life-threatening ventricular arrhythmias. Thus, genetic ventricular arrhythmia syndromes may provide an opportunity to gain mechanistic insight about SUDEP if brain seizures coexisted. However, the originally proposed pathophysiological mechanism which starts from a primary neuronal defect which leads to secondary cardio-respiratory arrest and dangerous cardiac arrhythmias could not be established in patients. As alternative, if an epileptogenic gene defect were expressed both in the brain and heart, this would allow for investigation of the underlying dysrhythmia mechanisms separately in the brain and heart, and be tested for mechanistic links between cortical hyperexcitability and sudden unexpected death by unknown neuro-cardiogenic mechanisms. Before I outline such novel epilepsy mechanisms with potential mechanistic links between the brain and the heart, I will review existing evidence about gene defects associated either with brain or heart dysrhythmias, to assess if common denominators exist which may contribute to seizure susceptibility.

2.1.2 Genes of fast neuronal signaling associated with epilepsy

The identification of genes that determine the risk of epilepsy has very important implications for patients, clinical diagnosis, and basic research. Within this context it is important to consider that molecular testing for genetic defects in epilepsy at current is mainly used by hypothesis driven research for the following two reasons: 1) genetic defects such as mutations can significantly increase our understanding of the basic mechanisms underlying seizure susceptibility; and 2) genetic defects which cause seizures in patients often lead to important research insights about the fundamental role of a protein which has previously not been fully understood in a neurophysiological context. Readers with a special interest in clinical diagnostic testing may also refer to the up-to-date special report of the International League Against Epilepsy (ILAE) Genetics Commission (Ottman et al.,2010).

In epilepsy, the majority of gene defects affect voltage- and/or ligand-gated ion channels that have been linked to paroxysmal network synchronization in seizure syndromes. These epileptogenic genes include both the pore-forming and regulatory subunits of Na^+, K^+, and Ca^{2+} channels of the plasma membrane, as well as ligand-gated channels modulated by GABA, Ach, and other ligands. Additionally, certain transport proteins are affected by genetic defects include the Na^+/K^+-ATPase and an important glucose transporter of the brain. While analysis of some of these epileptogenic gene mutations in heterologous cell expression systems has provided important insights, it is important to note that considerable gaps remain in our understanding how a specific channelopathy may result in increased network excitability and abnormal network synchronization in the brain. Therefore, it is without doubt very challenging to mechanistically understand epilepsy syndromes associated with other paroxysmal neuronal disorders or even other organ dysfunction like cardiac arrhythmias as a hypothetical cause of SUDEP. Table 1 on the following page summarizes confirmed genetic epilepsy syndromes, which have been mostly linked to defects in ion transport. Although we do not understand the precise mechanisms of abnormal network synchronization behind most of the defects listed in table 1, a common denominator of these epilepsy genes are fast neurophysiological signaling mechanisms.

Seizure syndromes that start within the first year of life				
Syndrome	**Gene**	**Protein**	**Defect**	**References**
Benign familial neonatal seizures	*KCNQ2*	Kv7.2	I(K) ↓	(Biervert et al., 1998; Charlier et al., 1998; Singh et al., 1998)
	KCNQ3	Kv7.2	I(K)	
Benign familial neonatal-infantile seizures	*SCN2A*	Nav1.2	I(Na)	(Berkovic et al., 2004; Heron et al., 2002)
Syndromes with prominent febrile seizures				
Syndrome	**Gene**	**Protein**	**Defect**	**References**
Dravet syndrome (severe myoclonic epilepsy of infancy)	*SCN1A*	Nav1.1	I(Na)	(Claes et al., 2001; Nabbout et al., 2003)
Genetic (generalized) epilepsy with febrile seizures plus (GEFS+)	*SCN1A*	Nav1.1		(Escayg et al., 2000)
	SCN1B	β1 SU		(Wallace et al., 1998)
	GABRG2	γ2 SU	$GABA_A$ receptor	(Baulac et al., 2001)
Childhood absence epilepsy with febrile seizures	*GABRG2*	γ2 SU		(Kananura et al., 2002; Wallace et al., 2001)
Idiopathic generalized epilepsies				
Syndrome	**Gene**	**Protein**	**Defect**	**References**
Early-onset absence epilepsy	*SLC2A1*	GLUT1	Glucose uptake ↓	(Suls et al., 2009)
Juvenile myoclonic epilepsy	*GABRA1*	α1 SU	$GABA_A$ receptor ↓	(Cossette et al., 2002; Suzuki et al., 2004)
Focal epilepsies				
Syndrome	**Gene**	**Protein**	**Defect**	**References**
Autosomal dominant nocturnal frontal lobe epilepsy	*CHRNA4*	α4 SU	nACh receptor	(Steinlein et al., 1995)
	CHRNB2	β2 SU		(De Fusco et al., 2000)
	CHRNA2	α2 SU		(Aridon et al., 2006)
Epilepsies associated with other paroxysmal disorders				
Syndrome	**Gene**	**Protein**	**Defect**	**References**
Generalized epilepsy and paroxysmal dyskinesia	*KCNMA1*	$K_{Ca}1.1$	I(K)	(Du et al., 2005)
Epilepsy with paroxysmal exercise-induced dyskinesia	*SLC2A1*	GLUT1	Glucose uptake ↓	(Suls et al., 2008; Weber et al., 2008)
Absence epilepsy and episodic ataxia	*CACNA1A*	Cav2.1	I(Ca, P/Q) ↓	(Imbrici et al., 2004; Jouvenceau et al., 2001)
Focal epilepsy and episodic ataxia	*KCNA1*	Kv1.1	I(K)	(Eunson et al., 2000; Spauschus et al., 1999; Zuberi et al., 1999)
Familial hemiplegic migraine and epilepsy	*ATP1A2*	Na^+,K^+-ATPase	I(K) ↓	(Deprez et al., 2008; Vanmolkot et al., 2003)

Table 1. Genes identified in idiopathic epilepsy syndromes. Abbreviations: I, indicates ionic current (type); ↑ gain-of-function; ↓ loss-of-function.

To compare the above identified mechanisms of epilepsy syndromes with those of paroxysmal arrhythmia syndromes of the heart, we will next review confirmed monogenetic disorders of the heart, which have also been linked to ion transport dysfunction. Please note, that for clarity this chapter is focused on genes underlying different forms of membrane transport defects in epilepsy or cardiac arrhythmias.

2.2.1 Genetic defects underlying cardiac dysrhythmias

Europe and North America have a high annual incidence of sudden cardiac death (SCD) amounting to up to 100 per 100.000 in the general population (Byrne et al., 2008; Chugh et al., 2004). SCD is defined as a sudden and unexpected pulseless primary cardiac event (Chugh et al., 2008). Despite the presence of modern resuscitation chains for out-of-hospital SCD the overall survival rate is only 4.6% (Nichol et al., 2008). SCD is the outcome of electrical heart disease that manifests as fast ventricular arrhythmias or pulseless electrical activity. In a significant number of patients, cardiac dysrhythmia and SCD occur unexpected without prior warning and without a clinically identifiable triggering mechanism. Therefore, cardiac dysrhythmia and SCD risk prediction remain a major challenge. However, understanding of molecular mechanisms has significantly advanced for inherited cardiac channelopathies that predispose to SCD (Lehnart et al., 2007).

Cardiac ion channelopathies provide important rationales to understand mechanisms of cardiac dysrhythmias and the risk of SCD. The most common cardiac genetic channelopathies manifest as delayed ventricular repolarization seen as a prolonged QT interval by surface electrocardiogram (ECG), fast ventricular arrhythmias, recurrent syncope (loss of consciousness), and seizures. The Long QT syndrome (LQTS) is mostly caused by genetic ion channel defects resulting in abnormal prolongation of the cardiac action potential in approximately 1 in 2000 mutation carriers (Roden, 2008). Depending on the underlying gene defect and incompletely understood environmental factors, LQTS mutation carriers have a significantly increased risk for fatal ventricular arrhythmias and SCD. The majority of identified LQTS mutations cause ion channel dysfunction through mutations of pore-forming α or accessory β subunits as summarized in table 2. A recently discovered LQTS variant phenotype is Sudden Infant Death Syndrome (SIDS) caused by some of the same gene defects. Among known cardiac ion channelopathies K^+ and Na^+ channel mutations of the *KCNQ1*, *KCNH2*, and *SCN5A* genes stand out, because these cause the great majority of LQTS cases.

Although seizures occur in LQTS mutation carriers, these were previously considered to represent secondary events due to reduced blood perfusion of the brain during cardiac arrhythmias. However, it can be difficult to distinguish between a phenotype of syncope from cardiac dysrhythmias and primary neurogenic seizure auras with or without myoclonus (McKeon et al., 2006). In addition, simultaneous electroencephalogram (EEG) and ECG recordings revealed a surprisingly high prevalence of up to 44% of different types of cardiac arrhythmias in individuals with primary epileptic seizures (Britton et al., 2006; Johnson et al., 2009; McKeon et al., 2006; Nei et al., 2000; Opherk et al., 2002; Zijlmans et al., 2002). Recently, seizure phenotypes have been reported in approximately one third of confirmed LQTS mutation carriers (including 22% with the most prevalent form LQTS1) suggesting that LQTS genes may cause neuronal hyperexcitability independent from cardiac arrhythmias (Johnson et al., 2009). In addition, seizures have been reported in up to half of confirmed *RYR2* mutation carriers affected by stress-induced ventricular arrhythmias (Postma et al., 2005). Of note, in a given mutation carrier neuronal seizures and cardiac arrhythmias may occur simultaneously, or a brain dysrhythmia may secondarily trigger a cardiac arrhythmia through unknown mechanisms.

Sudden infant death syndrome (SIDS): starting within the first year of life				
Syndrome	**Gene**	**Protein**	**Defect**	**References**
SIDS1	*KCNH2*	Kv11.1	I(Kr) ↓	(Arnestad et al., 2007)
SIDS2	*KCNQ1*	Kv7.1	I(Ks) ↓	(Moss et al., 2007)
SIDS3	*KCNJ2*	Kir2.1	I(K1) ↓	(Arnestad et al., 2007)
SIDS4	*SCN5A*	Nav1.5	I(Na) ↑	(Plant et al., 2006; Van Norstrand et al., 2008)
Long QT syndrome (LQTS): prominent lengthening of the electrocardiogram QT interval				
Syndrome	**Gene**	**Protein**	**Defect**	**References**
LQTS1	*KCNQ1*	Kv7.1	I(Ks) ↓	(Moss et al., 2007; Wang et al., 1996)
LQTS2	*KCNH2*	Kv11.1	I(Kr) ↓	(Curran et al., 1995)
LQTS3	*SCN5A*	Nav1.5	I(Na) ↑	(Bennett et al., 1995; Wang et al., 1995)
LQTS5	*KCNE1*	β SU	I(Ks) ↓	(Sanguinetti et al., 1996; Splawski et al., 1997)
LQTS6	*KCNE2*	β SU	I(Kr) ↓	(Abbott et al., 1999)
LQTS7	*KCNJ2*	Kir2.1	I(K1) ↓	(Bendahhou et al., 2003; Plaster et al., 2001)
LQTS8	*CACNA1C*	Cav1.2 α1c	I(Ca,L) ↑	(Splawski et al., 2005; Splawski et al., 2004)
LQTS10	*SCN4B*	β4 SU	I(Na) ↑	(Medeiros-Domingo et al., 2007)
Short QT syndrome (SQTS): prominent shortening of the electrocardiogram QT interval				
Syndrome	**Gene**	**Protein**	**Defect**	**References**
SQTS1	*KCNH2*	Kv11.1	I(Kr) ↑	(Brugada et al., 2004; Hong et al., 2005a)
SQTS2	*KCNQ1*	Kv7.1	I(Ks) ↑	(Bellocq et al., 2004; Hong et al., 2005b)
SQTS3	*KCNJ2*	Kir2.1	I(K1) ↑	(Priori et al., 2005)
SQTS4	*CACNA1C*	Cav1.2 α1c	I(Ca,L) ↓	(Antzelevitch et al., 2007)
SQTS5	*CACNB2*	β2b SU	I(Ca,L) ↓	(Antzelevitch et al., 2007)
Timothy Syndrome (TS) and Autism Spectrum Disorder				
Syndrome	**Gene**	**Protein**	**Defect**	**References**
TS1	*CACNA1CA*	Cav1.2 α1c	I(Ca,L) ↑	(Splawski et al., 2004)
TS2	*CACNA1C*	Cav1.2 α1c	I(Ca,L) ↑	(Splawski et al., 2005)
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)				
Syndrome	**Gene**	**Protein**	**Defect**	**References**
CPVT1	*RYR2*	RyR2	SR Ca leak ↑	(Laitinen et al., 2001; Priori et al., 2001)
CPVT2	*CASQ2*	Calsequestrin	SR Ca leak ↑	(Lahat et al., 2001; Postma et al., 2002)
CPVT3	*KCNJ2*	Kir2.1	I(K1) ↑	(Plaster et al., 2001; Tester et al., 2006)

Table 2. Genes identified in idiopathic ventricular arrhythmia syndromes. Abbreviations: I, indicates ionic current (type); SR, sarcoplasmic reticulum calcium store; ↑ gain-of-function; ↓ loss-of-function.

It is important to note that many genetic and phenotypic variations of cardiac channelopathy syndromes exist. In LQTS approximately 40% of family members who are confirmed carriers of a gene mutation are clinically silent with a normal or borderline QT interval (Bai et al., 2009; Hofman et al., 2007). In addition, some patients with borderline QT interval prolongation are negative for LQTS mutations, but positive for mutations linked to the syndrome CPVT (Tester et al., 2006; Tester et al., 2005). Furthermore, mutations in intronic regions have recently been identified as a cause of LQTS (Zhang et al., 2004). Of significance for molecular mechanisms, cardiac arrhythmias in LQTS1 and CPVT1 mutation carriers are both triggered by increased physical or emotional stress, indicating that the respective Kv7.1 and RyR2 defects may share the same regulatory pathways during arrhythmia triggers under control of the sympathetic nervous system (Lehnart et al., 2004). In contrast, LQTS3 mutation carriers experience cardiac arrhythmias during rest or sleep (Roden, 2008). Notably, for intermediate risk traits at the level of the general population genome-wide association studies have identified determinants of the QT interval including variants of the *KCNQ1*, *KCNH2*, and *SCN5A* genes (Albert et al.; Newton-Cheh et al., 2009). In analogy to the ILAE for epilepsy, the International Long QT Syndrome Registry facilitates insight and patient recommendations about genetic forms of cardiac arrhythmias (Moss & Schwartz, 2005).

2.2.2 Synopsis of existing genetic dysrhythmia mechanisms in the brain and heart

Excitability of the brain and heart is based on the same principles of ion transport. At the molecular level some of the same classes of ion channels, for example the *SCN* and *KCNQ* isoforms, exist in the brain and heart. However, comparison of tables 1 and 2 shows that previously established monogenic defects cannot readily provide a mechanistic association between neuronal and cardiac dysrhythmias. In addition, as outlined under 2.1.2 the prevailing research focus about a given organ disease like cardiac arrhythmias may introduce a phenotypic bias such that other organs like brain seizures may have not been comprehensibly studied. Indeed, prior to the age of genetic information epilepsy patients with frequent seizures were sometimes diagnosed with the syndrome of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), however, the arrhythmias were thought to explain the seizure phenotype and epilepsy treatment was discontinued (Leenhardt et al., 1995). Within this context it is important to realize that the differential diagnosis of brain and heart seizure phenotypes is of historical significance and extends to famous scholars and patients including Napoleon Bonaparte (Osler, 1903). Thus, one must consider that accurate differentiation between neuronal and cardiac seizure phenotypes is challenging in patients and may need patience (McKeon et al., 2006).

Despite these difficulties, initial clues that LQTS gene mutations may also cause seizures originating from the brain came from studies of the cardiac sodium channel Nav1.5. As outlined in table 2, *SCN5A* mutations cause LQTS including ventricular arrhythmias and SCD (Chen et al., 1998; Wang et al., 1995). In addition, Nav1.5 is expressed in the entorhinal cortex and the amygdala, and other limbic brain regions which have been associated with a low threshold for abnormal network synchronization and brain seizures (Hartmann et al., 1999). Despite these early hypothetical associations, cardiac LQTS genes have subsequently not been mechanistically linked to the context of primary brain dysrhythmias. Therefore, despite a wealth of molecular and electrophysiological insights originating from genetic linkage studies, prediction and prevention of associated brain and heart dysrhythmias

remain little understood. Clearly, additional and likely complex studies which integrate multiple investigative levels are needed, in particular to explore underlying mechanisms of potentially co-existing brain and heart dysrhythmias, and to elucidate mechanistic links between electrical brain and heart phenotypes. As will be discussed next, recent basic science research studies suggest an unprecedented level of complexity concerning ion transport dysfunction and molecular crosstalk within the context of excitable organ disease of the brain and heart.

2.3 Novel genetic mechanisms of associated brain and heart dysrhythmias

Completely new epilepsy mechanisms have recently been identified in mouse models with human cardiac arrhythmia symptoms of confirmed mutation carriers. Of note, through a bench-to-bedside approach these experimental studies strongly suggest that combined neuro-cardiogenic disease mechanisms exist. These neuro-cardiogenic syndromes may in principle also underlie SUDEP in patients. Notably, combined neuro-cardiogenic mechanisms have been implicated earlier in the genetic Timothy syndrome, a rare ion channelopathy causing multiple organ phenotypes including cardiac arrhythmias, autism, mental retardation and seizures. Patients with Timothy syndrome have de novo mutations of splice exon 8A of the main cardiac L-type Ca^{2+} channel pore-forming α-subunit Cav1.2 resulting in intracellular Ca^{2+} overload, which occurs in the heart and brain (Splawski et al., 2005). While the patient phenotype of Timothy syndrome is very complex due to multiple coexisting organ and metabolic disease processes, which makes elucidation of specific molecular SUDEP mechanisms difficult, it emphasizes the importance to consider both the brain and heart in seizure phenotypes.

Abnormal intracellular Ca^{2+} homeostasis has also been identified for a different epileptogenic mechanism due to mutations of the cardiac ryanodine receptor type 2 (RyR2). RyR2 forms the α-subunit of the tetrameric intracellular Ca^{2+} release channel, and is highly expressed in the heart and brain. In 2001 RyR2 missense mutations were identified in patients with syncope, seizures and SCD (Laitinen et al., 2001; Priori et al., 2001). Due to the characteristic dependence of the cardiac phenotype on physical and/or emotional stressors, the syndrome has been called Catecholaminergic Polymorphic Ventricular Tachycardia type 1 (CPVT1) (Priori et al., 2001). The phenotype of stress-induced cardiac arrhythmias is dependent on heart rate and reproducible for diagnostic purposes by exercise ECG testing in RyR2 mutation carriers (Lehnart et al., 2004). It has been assumed that in CPVT the syncope and seizures are not of primary neuronal origin, but due to decreased blood perfusion of the brain during ventricular arrhythmias (also known as Stokes-Adams attack)(Leenhardt et al., 1995). However, under experimentally controlled conditions behavioural and electrophysiological analysis of knockin mice with RyR2 missense mutations have shown that generalized seizures can occur independent from cardiac arrhythmias (Lehnart et al., 2008). As will be discussed below, RyR2 mutant mice provided the first evidence that the same molecular ion channel defect can cause generalized seizures and ventricular arrhythmias. RyR2 mutations cause abnormal intracellular Ca^{2+} signals in neurons and cardiac myocytes, which represents a novel genetic candidate mechanism of generalized seizures and of unexpected death in epilepsy.

Recently, a second mechanism of generalized seizures and cardiac arrhythmias has been identified in mice with *KCNQ1* mutations, which affects the pore-forming α-subunit of the cardiac delayed rectifier K^+ channel Kv7.1 (table 2). Kv7.1 forms the slow repolarizing

membrane current I(Ks), which is active during the repolarizing phases 2 and 3 of the cardiac action potential. Kv7.1 loss-of-function mutations increase cardiac action potential duration (Wang et al., 1996; Wang et al., 1999; Westenskow et al., 2004). Kv7.1 mutations underlie the most common form of the cardiac Long QT syndrome (LQTS1) leading to syncope, stress-induced arrhythmias, seizures and SCD. Mouse models harbouring patient missense mutations of the *KCNQ1* gene have reproduced key aspects of the human cardiac LQTS1 phenotype (Casimiro et al., 2004). In addition, the LQTS1 mouse models reproduce sensory defects of the inner ear hair cells, which also express Kv7.1 channels (Casimiro et al., 2004; Kubisch et al., 1999). As will be discussed below, Noebels and colleagues have recently re-evaluated the same KCNQ1 knockin mice with patient missense mutations and identified a previously unknown generalized seizure phenotype (Goldman et al., 2009).

The same gene defects which have originally been identified in patients with cardiac arrhythmia phenotypes in the LQTS1 and CPVT1 syndromes, have recently been associated with generalized seizure phenotypes in the respective *KCNQ1* and *RYR2* knock in mouse models with patient mutations (Goldman et al., 2009; Lehnart et al., 2008). While LQTS1 mutations of Kv7.1 lead to prolongation of the cardiac action potential, CPVT1 mutation of RyR2 result in abnormal cardiac membrane depolarizations following the regular cardiac action potential, referred to as delayed afterdepolarizations (DADs). Notably, the clinical phenotypes of LQTS1 and CPVT1 patients both include syncope and seizures, which as mentioned earlier can be difficult to differentiate (McKeon et al., 2006). Indeed, in LQTS1 seizures have been reported in up to one-third of genotype-confirmed patients (Johnson et al., 2009) and in CPVT1 in up to half of confirmed RyR2 mutation carriers (Postma et al., 2005). Thus, genetic patient studies have shown that both LQTS1 and CPVT1 mutation carriers exhibit symptoms of neuronal hyperexcitability.

Despite significant conceptual advances through recent identification of ion channel gene variants, which cause combined seizure and arrhythmia syndromes, many questions remain unanswered and require further study. These questions concern the specific brain regions and neuron types, which show a decreased threshold for aberrant network synchronization, such that prolonged depolarization or delayed repolarization may initiate primary brain seizures. In addition, arrhythmias in LQTS1 and CPVT1 are characteristically modulated by the autonomous nervous system. If the autonomous nervous system is also affected by the same genes and modulates the phenotype defects needs further exploration. The following chapters will discuss recent advances in ion channel studies related to epilepsy and particular insight about combined neuro-cardiogenic phenotypes and mechanisms which may link the dysrhythmia phenotypes of the two separate organs. Already, these recent insights have motivated further research about diagnostic strategies to improve risk prediction and prevention in patients with seizure disorders of unknown origin. In addition, novel therapeutic strategies targeting the underlying molecular mechanisms are under development. Therefore, the following chapters will also discuss the translation of novel seizure mechanisms in neuro-cardiogenic syndromes into therapeutic rationales.

2.3.1 Ryanodine receptor mutations cause generalized seizures

Seizure models using pharmacological inducers have found intracellular Ca^{2+} abnormalities in inhibitory interneurons and astrocytes during seizure like activity (Tian et al., 2005). In addition, inositol 1,4,5-trisphosphate receptor type 1 (IP3R1) intracellular Ca^{2+} release channels, which localize to intracellular ER Ca^{2+} stores, have been associated with seizures

in mice (Street et al., 1997). However, a mechanistic relationship between dysfunction of intracellular Ca^{2+} release channels and seizures has not been established. Ca^{2+} is an important neuronal signaling molecule and intracellular Ca^{2+} release channels are an important source including IP3R1-3 isoforms (Mignery et al., 1989; Street et al., 1997) and the related ryanodine receptor isoforms (RyR1-3)(Henzi & MacDermott, 1992; Kostyuk & Verkhratsky, 1994). Interestingly, mutation carriers with RyR2 mutations have been shown to exhibit syncope, seizures and cardiac arrhythmias (Postma et al., 2005).

RyR2 is the major Ca^{2+} release channel of the heart. Over 100 different *RYR2* mutations have been associated with Catecholaminergic Polymorphic Ventricular Tachycardia type 1 (CPVT) and ventricular arrhythmias (table 2). Importantly, early clinical descriptions of childhood CPVT documented initial presentations with seizures, loss of consciousness, convulsions, and involuntary incontinence in approximately 50% of patients (Leenhardt et al., 1995). A similar presentation has been confirmed in *RYR2* mutation carriers who have also presented with seizures in 50% of patients (Postma et al., 2005). Additionally, patients with CPVT2 caused by calsequestrin2 mutations also have seizures (Lahat et al., 2001). Indeed, RyR2 is highly expressed in the brain including the hippocampus dentate gyrus granule cell layer and the CA1-3 pyramidal cell layers (figure 1). These hippocampal areas have been associated with pharmacologically stimulated ryanodine receptor dysfunction and generalized tonic-clonic seizure activity (Mori et al., 2005).

We created knockin mice with RyR2 patient missense mutations (R2474S and N2386I) which have been linked to autosomal-dominant CPVT in families (Priori et al., 2001). The heterozygous *RYR2* mutant mice spontaneously developed recurring generalized tonic-clonic seizures during arousal as well as in the absence of obvious environmental changes. Generalized myoclonic seizures in *RYR2* mutant mice exhibited a rapid progression from freezing to partial behavioral abnormalities to generalized myoclonic and tonic-clonic behavior (Lehnart et al., 2008). Video-assisted analysis showed that generalized seizure activity lasted between 20 and 120 seconds. Simultaneous EEG-ECG recording showed bilateral voltage discharges including higher frequency sharp spikes and waves, however, no cardiac arrhythmias (figure 1; *lower, left*). These data unambiguously show that at least some of the seizures in *RYR2* mutation carriers are of primary neuronal origin. Importantly, recent studies have confirmed the a seizure phenotype in patients including *RYR2* mutation carriers (Johnson et al.,2009; Nagrani et al.,2011).

Pharmacological challenge with the seizure inducing drugs 4-aminopyridine and caffeine showed increased seizure susceptibility in *RYR2* mutant mice. Generalized tonic-clonic seizures occurred significantly earlier in *RYR2* mutant as compared to wild-type control mice. In addition, *RYR2* mutant mice showed a faster progression to more severe seizure stages. Moreover, the seizure phenotype was found in two independently generated *RYR2* mutant knockin mouse strains (R2474S and N2386I).

Extracellular local field potential (LFP) recording in acute hippocampal brain slices revealed significantly increased excitability following 4-aminopyridine treatment in *RYR2* mutant brain tissue as compared to wild-type control tissue sections (Lehnart et al., 2008). LFP recording showed discharges with higher burst frequency and duration in CA3 network regions of *RYR2* mutant brain tissue (figure 1; *lower, center*). Increased hippocampal CA3 seizure activity of *RYR2* mutant cells has been confirmed with confocal Ca^{2+} imaging of the somata in the principal cell layer in hippocampal brain slices (figure 1; *lower, right*). The Ca^{2+}

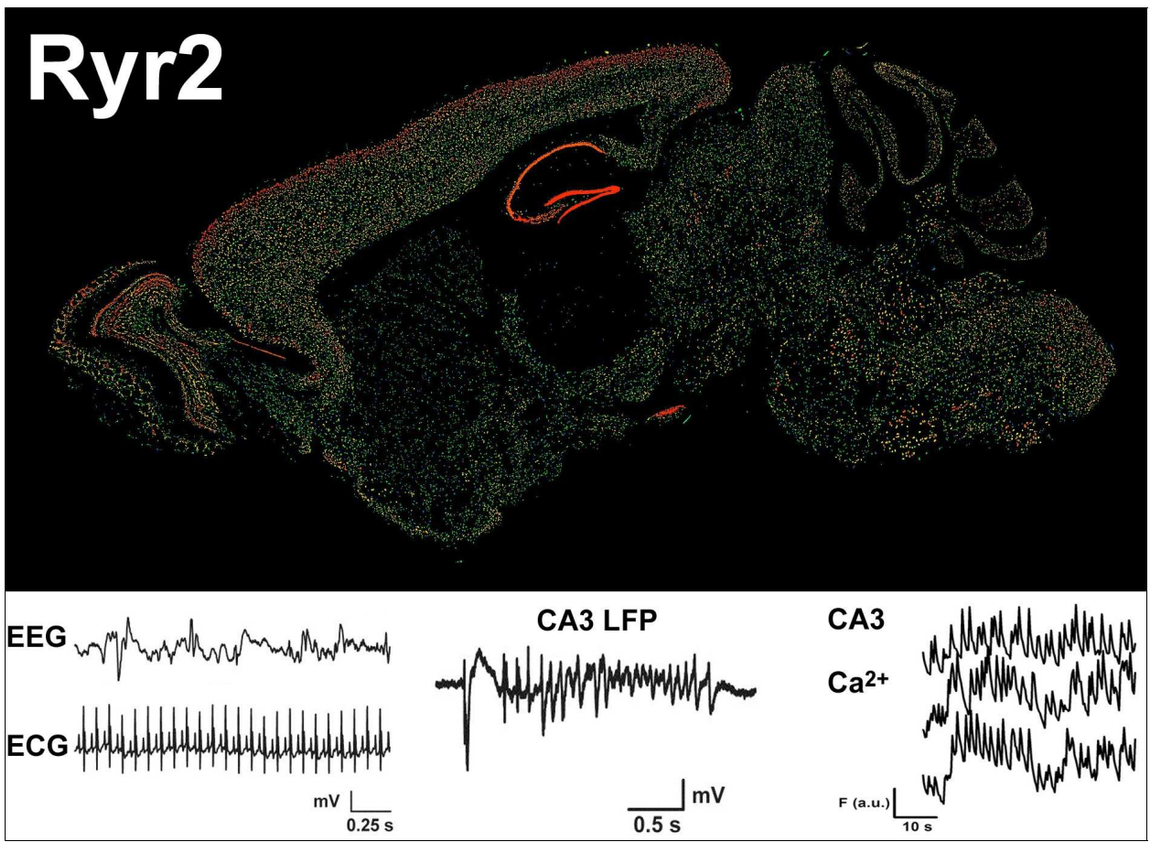

Fig. 1. Epileptogenic phenotype of *RYR2* knockin mice with orthologous patient mutations. *Top*: In situ RyR2 hybridization of a sagittal brain section from an adult male mouse brain. Red colour indicates maximal RyR2 mRNA expression as evidenced in the hippocampus and cerebral cortex. Image was prepared with the Allen Brain Atlas: http:www.brain-map.org; Seattle, WA: Allen Institute for Brain Science © 2006. *Bottom, left*: simultaneous EEG-ECG recording of awake heterozygous RyR2-R2474S mouse during start of generalized myoclonic seizure. *Bottom, center*: extracellular local field potential (LFP) recording of seizure-like events from CA3 region of hippocampal slices incubated in 10 µM 4-aminopyridine from heterozygous RyR2-R2474S mutant adult mouse showing abnormally complex and sustained bursting activity as compared to wild-type control (not shown). *Bottom, right*: continuous confocal fluo-4 Ca^{2+} fluorescence imaging of RyR2-R2474S mutant CA3 principal cell layer showing synchronized seizure bursting activity in low Mg^{2+} (0.5 mM)/high K^{+} (8.5 mM) solution. Each trace represents the cytosolic Ca^{2+} signal from a local region of interest corresponding to the somata of three neighbouring CA3 pyramidal neurons. Reproduced from (Lehnart et al., 2008) with permission by "The American Society of Clinical Investigation" (www.jci.org) provided by Copyright Clearance Center, 2011.

imaging experiments revealed increased neuronal network synchronization in the CA3 region consistent with increased bursting activity of CA3 cells by LFP recording. In addition, single-channel bilayer recording, which were isolated from hippocampal tissue, showed a gain-of-function defect of RyR2-R2474S mutant channels consistent with abnormal intracellular Ca^{2+} leak, and consistent with abnormal confocal Ca^{2+} bursting activity in RyR2-R2474S brain slices (Lehnart et al., 2008). Because heterozygous RyR2-R2474S mice exhibited recurrent generalized

tonic-clonic seizures and bilateral cortical EEG discharges in the absence of cardiac arrhythmias and in addition stress-induced ventricular arrhythmias in the absence of seizure activity, we proposed that RyR2 mutations cause a combined neuro-cardiogenic syndrome (Lehnart et al., 2008). As CPVT mutation carriers experience a very high mortality rate at young age which has been estimated between 33% and 50% at 35 years (Lehnart et al., 2004; Priori et al., 2002), *RYR2* is is a potential candidate gene for SUDEP.

2.3.2 Potassium channel mutations and generalized seizures

Unexpectedly, a LQTS patient study found that one third of confirmed mutation carriers have seizures including the relatively common *KCNQ1* mutation, indicating a potential link between cardiac arrhythmias and epilepsy (Johnson et al., 2009) However, *KCNQ1* expression in the brain is incompletely understood partially due to conflicting data. Importantly, *KCNQ1* mRNA and Kv7.1 protein expression, as well as expression of the accessory β-subunit minK have recently been confirmed in the human and mouse brain in the cortex and hippocampus (Goldman et al., 2009). Immunofluorescence staining as shown in figure 2 (*left*) further demonstrated that Kv7.1 is expressed within important hippocampal pathways including pyramidal neurons of the CA1 and CA3 regions, granule cells of the dentate gyrus, and hilar interneurons (Goldman et al., 2009). In addition, Kv7.1 positive neurons were found in the cortex, the thalamus, as well as brain stem nuclei which contribute parasympathetic outflow to the heart by the vagus nerve (Goldman et al., 2009). Thus, Kv7.1 protein expression has been confirmed in specific brain regions of the adult mouse, which are of potential significance for epileptogenesis.

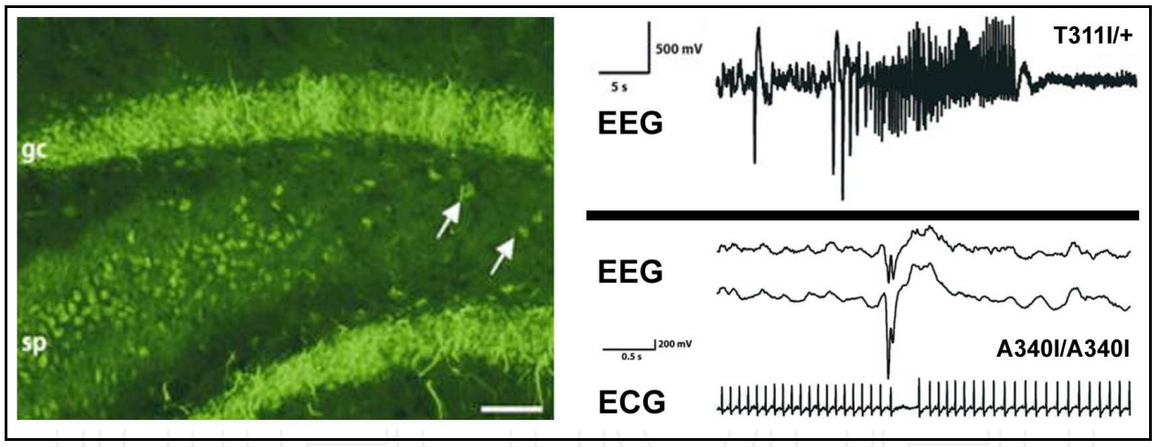

Fig. 2. Epileptogenic phenotype of *KCNQ1* knockin mice with orthologous patient mutations. *Left*: Kv7.1 immunofluorescence image of adult mouse brain section of the hippocampus dentate gyrus/hilar region showing positively stained granule cell layer (gc), CA3 pyramidal cell layer (sp), and hilar interneurons (arrows). Scale bar indicates 50 µm. *Right top*: EEG recording of a heterozygous Kv7.1-T311I mutant mouse during onset of a spontaneous convulsive seizure attack. *Right bottom*: Detail of combined EEG and ECG recording of a homozygous Kv7.1-A340I mutant mouse showing bilateral interictal discharges over the temporal cortex with coinciding AV conduction block in the ECG. Reproduced from (Goldman et al.,2009) with permission by "The American Association for the Advancement of Science" (www.sciencemag.org) provided by Copyright Clearance Center, 2011.

Two knockin mouse lines (T311I and A340E) with *KCNQ1* point mutations corresponding to human mutation carriers have previously been shown to reproduce the cardiac phenotype of LQTS1 (table 2) including ventricular arrhythmias (Casimiro et al., 2004). In addition, video-monitoring showed spontaneously occurring generalized seizures in one third of heterozygous mutant *KCNQ1* knockin mice, but never in wild-type control animals (Goldman et al., 2009). In addition, all heterozygous *KCNQ1* mutant animals showed partial seizures lasting less than 10 secs. The generalized seizures were characterized by sudden arrest of activity, followed by tonic extension and whole body convulsive movements, and simultaneous EEG showed bilateral rhythmic high voltage sharp wave discharges evolving into a higher frequency rhythmic discharges (figure 2, *right top*). In contrast, the partial seizures were characterized by behavioural arrest without prominent clonic movements, and the EEG showed coinciding low-voltage rhythmic slow activity interspersed with spike and wave discharges.

Registration of cortical activity by EEG in *KCNQ1* knockin mice with Kv7.1 mutations revealed epileptiform spike discharges and simultaneous ECG recording showed abnormal cardiac events consistent with slowing of the heart rhythm (Goldman et al., 2009). Awake, freely moving *KCNQ1* knockin mice exhibited frequent bilateral interictal epileptiform discharges including sharp waves and spikes, and prolonged runs of temporal focal slow waves. Interestingly, simultaneous ECG recording showed that approximately one fourth of cortical EEG discharges coincided with cardiac ECG abnormalities including prolonged beat-to-beat intervals, extrabeats, and even asystolie (complete block of ventricular rhythm) as shown figure 2 (*right bottom*). Of note, 62% of ECG abnormalities coincided with cortical EEG changes. Simultaneous EEG-ECG abnormalities are in agreement with autonomic dysregulation of impulse conduction as previously reported in SUDEP patients (Nei et al., 2004). In addition SCD was found in one homozygous T311I mouse, which died spontaneously from cardiac asystolie following prolonged seizures (Goldman et al., 2009).

2.4 Novel, targeted treatment strategies

Significant progress has been made to understand epilepsy through studies of monogenetic syndromes and the associated molecular mechanisms of seizures. Epilepsy genes have been identified in human mutations carriers and increasingly through animal models with distinct seizure phenotypes. Notably, the majority of identified epilepsy genes encode ion channels and associated subunits. These important insights have provided candidate treatment targets based on identified cellular and molecular mechanisms of epileptogenesis. In addition, epilepsy is increasingly recognized as heterogeneous syndrome of co-existing and even multi-organ syndromes, for example the neuro-cardiogenic syndromes discussed above. Advanced understanding of basic and complex seizure mechanisms has triggered development of new diagnostic and therapeutic approaches some of which are summarized here in the context of ion channelopathies.

Existing pharmacological and surgical therapies have been estimated to control seizure symptoms in approximately 60% of epilepsy patients. Therefore, development of novel therapies remains a major challenge. If one considers combined neuro-cardiogenic syndromes in the context of pharmacotherapies several important perspectives can be drawn from the mechanistic insights discussed in earlier chapters. Individuals at risk with SUDEP represent a major clinical challenge, and the gray area of undetected cardiac arrhythmia risk is potentially high due to lack of adequate screening strategies and

awareness. Recent ECG studies showed that every fifth epilepsy patients experiences abnormally slow heart rhythms during seizures, culminating in 16% with asystolie which is potentially lethal (Rugg-Gunn et al., 2004). For confirmed *KCNQ1* mutation carriers implantable pacemaker therapy should be considered in the context of abnormally slow heart rhythms, and considering the possible changes of brainstem parasympathetic outflow to the heart recently identified in knockin mice with Kv7.1 mutations (Goldman et al., 2009). As β-blockers are therapeutically recommended in LQTS1 in confirmed *KCNQ1* mutation carriers with the potential side effect of slow heart rates, it is important to carefully monitor the heart rate behaviour in affected patients (Roden, 2008).

In addition, we have developed novel RyR2-specific compounds which permeate the blood-brain barrier and inhibit both neuronal seizures and cardiac arrhythmias (Lehnart et al., 2008). Different from conventional ion channel blockers, RyR2 stabilizing compounds like S107 have no effect on physiological channel function and do not alter intracellular Ca^{2+} signaling (Lehnart, 2007). In addition, S107 has not shown any significant side effects against other ion channels or enzymes in large screening panels (Lehnart et al., 2008). Similar to LQTS1, β-blocker therapy is recommended in patients with CPVT1 and confirmed *RYR2* mutation carrier status due to the characteristic dependence of cardiac arrhythmias on sympathetic outflow to the heart. In summary, the neuro-cardiological implications of idiopathic epilepsies are potentially important in mutation carriers, and comprehensive phenotype and genotype risk profiling may lead to improved therapy and prevention of fatal arrhythmias in affected epilepsy patients.

2.5 Summary of combined syndromes of neuronal and cardiac ion channelopathies

Recent studies have for the first time identified previously unrecognized brain ion channelopathies as the neurobiological basis of generalized seizures. While the epilepsy phenotypes represent primary brain discharges, the same molecular defects precipitate life-threatening cardiac arrhythmias. The following mechanisms have been proposed to underlie epilepsy in combined neuro-cardiogenic syndromes:

Kv7.1 dysfunction in *KCNQ1* mutation carriers with LQTS1 may alter the propensity of neurons and cardiac myocytes to repolarize following depolarization by an action potential. This results in a decreased repolarization capacity in the brain and heart. In the brain, a decreased repolarization capacity during action potential firing may result in seizures and brainstem autonomic dysfunction of parasympathetic outflow leading to heart rhythm block and asystolie for example at the level of the cardiac AV node. Dysfunction of brain stem parasympathetic outflow to the cardiac sinus and atrioventricular nodes as a cause of asystolie in epilepsy expands previously described arrhythmia mechanisms, since fast ventricular arrhythmias are characteristically triggered by increased sympathetic outflow in *KCNQ1* mutation carriers. Because Kv7.1 mutations can cause dangerous cardiac arrhythmias, *KCNQ1* is a molecular candidate mechanism and risk factor of SUDEP. These findings establish *KCNQ1* in neuronal hyperexcitability and epileptogenesis. Hundreds of *KCNQ1* mutations have been identified mostly leading to loss-of-function phenotypes. However, the correlation between Kv7.1 channel defects and the clinical phenotype in different organs is variable, and not all mutations may cause epilepsy or only when a permissive background or environmental condition exists.

RYR2 mutations appear to cause increased neuronal burst activity of the hippocampal CA3 region and seizure activity as evidenced by synchronous bursting Ca^{2+} signals of principal

cells in hippocampal brain slices. Indeed, increased neuronal network synchronization in the CA3 region is consistent with a gain-of-function defect of RyR2-R2474S mutant channels which exhibit defective closure (Lehnart et al., 2008). A hippocampal seizure mechanism is also consistent with the progressive, generalized tonic-clonic seizures and bilateral cortical EEG discharges documented in *RYR2* mutant mice with patient mutations.

3. Conclusion

Recent advances in ion channelopathy studies related to epilepsy have achieved important new insights about combined neuro-cardiogenic phenotypes, and mechanisms which may link dysrhythmia phenotypes of the brain and heart through the autonomic nervous system. Already, these insights have motivated further research about diagnostic strategies to improve risk prediction and prevention in patients with seizure disorders of unknown origin. In addition, novel therapeutic strategies which target the underlying molecular mechanisms are under development. Despite significant new mechanistic insight about Kv7.1 and RyR2 ion channel mutations as the cause of combined neuro-cardiogenic seizure and arrhythmia syndromes, many questions remain unanswered and require further study. These questions concern the specific brain regions and neuron types, which show a decreased threshold for aberrant network synchronization, such that prolonged depolarization or delayed repolarization may initiate primary brain seizures. In addition, arrhythmias in LQTS1 and CPVT1 are characteristically modulated by the autonomous nervous system. If the autonomous nervous system is also affected by the same gene mutations and exacerbates the cardiac and/or neuronal phenotypes needs further exploration through multidisciplinary research teams. Clearly, the new insights about neuro-cardiogenic dysrhythmias should motivate both clinicians and researchers to critically inquire complex phenotypes beyond the borders of a given research discipline.

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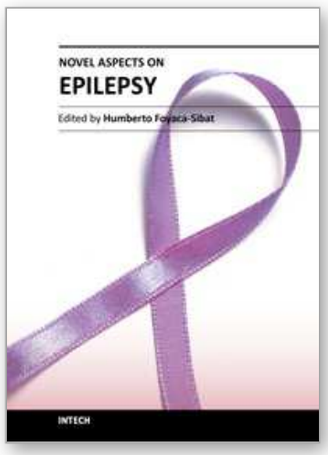

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This book covers novel aspects of epilepsy without ignoring its foundation and therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis as a leading cause of epilepsy in developing countries. We are looking forward with confidence and pride in the vital role that this book has to play for a new vision and mission. Therefore, we introduce novel aspects of epilepsy related to its impact on reproductive functions, oral health and epilepsy secondary to tuberous sclerosis, mithocondrial disorders and lisosomal storage disorders.

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