Author/s:
Li, MCH;O'Brien, TJ;Todaro, M;Powell, KL

Title:
Acquired cardiac channelopathies in epilepsy: Evidence, mechanisms, and clinical significance

Date:
2019-09-01

Citation:
Li, M. C. H., O'Brien, T. J., Todaro, M. & Powell, K. L. (2019). Acquired cardiac channelopathies in epilepsy: Evidence, mechanisms, and clinical significance. Epilepsia, 60 (9), pp.1753-1767. https://doi.org/10.1111/epi.16301.

MR. MICHAEL CHAO HAO LI (Orcid ID : 0000-0002-0616-1599)

Article type : Critical Review – Invited Commentary

Title: ACQUIRED CARDIAC CHANNELOPATHIES IN EPILEPSY: EVIDENCE, MECHANISMS AND CLINICAL SIGNIFICANCE.

Authors:

1. Michael CH Li[1,2]
2. Terence J O'Brien[1,2]
3. Marian Todaro[1,2,3]
4. Kim L Powell[1]

[1] Department of Neuroscience, Central Clinical School, Monash University

[2] Department of Medicine, Royal Melbourne Hospital, University of Melbourne

[3] Department of Neurology, Royal Melbourne Hospital

Corresponding author's contact information:

Name: Dr Kim Powell

Address: Department of Neuroscience,
Central Clinical School, Monash University
The Alfred Centre, Level 6
99 Commercial Road, Melbourne VIC 3004, Australia

Phone number: +61 3 9903 0856 Email: kim.powell@monash.edu

Key words: ion channel, remodelling, conduction, sudden cardiac death, arrhythmia, seizures, epilepsy

Number of pages: 26

Number of words: 4927

Number of references: 98

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/EPI.16301

Number of figures: 4

Number of tables: 1

Supporting Information: Supplementary Table 1, Supplementary Table 2

Summary:

There is growing evidence that cardiac dysfunction in patients with chronic epilepsy could play a pathogenic role in sudden unexpected death in epilepsy (SUDEP). Recent animal studies have revealed that epilepsy secondarily alters the expression of cardiac ion channels alongside abnormal cardiac electrophysiology and remodelling. These molecular findings represent novel evidence for an acquired cardiac channelopathy in epilepsy, distinct from inherited ion channels mutations associated with cardio-cerebral phenotypes. Specifically, seizure activity has been shown to alter the mRNA and protein expression of voltage-gated sodium channels ($Na_v1.1$, $Na_v1.5$), voltage-gated potassium channels ($K_v4.2$, $K_v4.3$), sodium-calcium exchangers (NCX1), and non-specific cation-conducting channels (HCN2, HCN4). The pathophysiology may involve autonomic dysfunction and structural cardiac disease – as both are independently associated with epilepsy and ion channel dysregulation. Indeed, *in vivo* and *in vitro* studies of cardiac pathology reveal a complex network of signalling pathways and transcription factors regulating ion channel expression in the setting of sympathetic overactivity, cardiac failure and hypertrophy. Other mechanisms such as circulating inflammatory mediators or exogenous effects of anti-epileptic medications lack evidence. Moreover, an acquired cardiac channelopathy may underlie the electrophysiological cardiac abnormalities seen in chronic epilepsy, potentially contributing to the increased risk of malignant arrhythmias and sudden death. Therefore, further investigation is necessary to establish whether cardiac ion channel dysregulation similarly occurs in patients with epilepsy, and to characterise any pathogenic relationship with SUDEP.

Key words: Ion channel, remodelling, conduction, sudden death, arrhythmia, seizures

1. Introduction

There is increasing clinical and experimental evidence that cardiac dysfunction occurs in patients with chronic epilepsy, and could play an important role in the pathophysiology of sudden unexpected death in epilepsy (SUDEP).[1] SUDEP is defined as death occurring in epilepsy in the absence of a known attributable cause,[1] and ranks second only to stroke when

comparing potential life-years lost across neurological conditions.[2] Patients with drug-resistant epilepsy and those who suffer frequent generalized tonic-clonic seizures are at greatest risk of SUDEP.[2] The potential significance of epilepsy-related cardiac dysfunction is highlighted by evidence of (i) ictal, (ii) interictal, and more recently, (iii) molecular abnormalities of the heart in epilepsy.[3]

Studies involving patients with chronic epilepsy demonstrate disturbances in cardiac rate, rhythm and repolarization during seizures. Changes in ictal heart rate indicate a degree of autonomic dysfunction, with tachycardia accompanying almost 60% of epileptic seizures and bradycardia occurring in up to 6% of focal seizures.[4,5] Moreover, around 14% of patients with refractory epilepsy exhibit serious electrocardiographic (ECG) abnormalities such as T-wave disturbances, ST elevation, and asystole.[5] Though these abnormalities have been reported in cases of SUDEP, it remains unclear whether they can precipitate a fatal event.[1] Seizure activity is also associated with lengthening or shortening of the QT interval corrected for heart rate (QTc), reflecting a disruption of ventricular repolarization that may predispose patients to ventricular arrhythmias.[4]

Aside from peri-ictal abnormalities, interictal observations reveal a baseline level of persistent cardiac dysfunction among individuals with epilepsy. As with ictal studies, interictal prolongation of the QTc interval has been reported, especially among individuals with poor seizure control.[6] Elevated sympathetic and decreased parasympathetic tone are also evident upon interrogation of heart rate variability, with a more severe dysautonomia noted in cases of SUDEP.[7,8] Furthermore, echocardiographic features of systolic and diastolic dysfunction highlight the functional consequences of myocardial damage secondary to repetitive ictal activity.[9–11] Together, these abnormalities may reflect a degree of underlying cardiac pathology in epilepsy.

Significantly, recent animal studies have reported changes in the transcription and translation of cardiac ion channels secondary to epileptogenesis, accompanied by abnormal cardiac electrophysiology.[12–16] This has led to the hypothesis that epilepsy secondarily alters cardiac ion channel expression, generating a chronic pro-arrhythmic state that increases the risk of sudden cardiac death or SUDEP. While the pathophysiology of an acquired cardiac channelopathy in epilepsy is unclear, candidate mechanisms include autonomic dysfunction and structural remodelling, given their associations with both seizure activity and cardiac ion channel dysregulation.[9,15,17] Indeed, the potential relevance of molecular cardiac dysfunction

is highlighted by a complex relationship between epilepsy, ion channel mutations, arrhythmogenic disorders and sudden death.[18,19]

Given that ictal and interictal cardiac abnormalities have been extensively reviewed elsewhere,[3] this review will focus on recent evidence for an acquired cardiac channelopathies in patients with chronic epilepsy. Possible underlying mechanisms are explored, including intracellular pathways which may mediate ion channel dysregulation. Finally, the potential clinical significance of molecular cardiac dysfunction in epilepsy is discussed.

2. Methods

To identify relevant articles, a comprehensive search of the Pubmed database was conducted from the beginning of indexed records to November 1st, 2018. Key search terms included "epilepsy/seizures", "cardiac/heart", "(ion) channel", "sudden (cardiac) death/SUDEP", "protein/mRNA", "expression/regulation", "transcription", "arrhythmia", "heart failure/hypertrophy/cardiomyopathy" and "drug/medication/anti-convulsant". To locate studies involving specific ion channel subtypes, the search phrase "SCN* OR KCN* OR HCN* OR CACN* OR SLC* OR NCX* OR Na_v* OR K_v* OR Ca_v*" (where * represents the truncation/wildcard operator) was utilized in conjunction with combinations of search terms. Reference lists of articles were searched to source additional articles.

3. Altered cardiac ion channel expression in epilepsy

3.1 Evidence from animal studies

Emerging evidence from animal studies indicates that epilepsy may alter the transcriptional expression of ion channels in cardiomyocytes. To date, ion channels implicated include hyperpolarization-activated cyclic nucleotide–gated (HCN) channels, voltage-gated potassium channels, voltage-gated sodium channels, and sodium-calcium exchangers as illustrated in Figure 1.[12–16] Significantly, this may represent a previously unappreciated form of secondary cardiac dysfunction in epilepsy.

HCN channels conduct an inward depolarising Na^+/K^+ current (I_f) in response to hyperpolarisation, contributing to cardiac and neuronal pacemaking, and setting of resting membrane potential.[20] Cardiac expression of HCN2 messenger RNA (mRNA) was decreased in all chambers except right ventricle, in both rats modelling acquired epilepsy (post-status epilepticus (SE) model) and genetic epilepsy (GAERS model).[13] Left ventricular HCN2 protein expression was also reduced in both animal models of epilepsy. Accompanying ECG

abnormalities included higher heart rate and QTc prolongation. Both models also showed increased beat-to-beat variability which normalised with isoprenaline (β-agonist) treatment, a finding mirrored in HCN2-knockout mice,[21] implying a potential link between the acquired HCN2 channelopathy and cardiac phenotype. Importantly, molecular and electrophysiological changes were i) consistent across different models of epilepsy, ii) temporally associated with seizure onset, and iii) persisted for at least 9-10 weeks.[13] Together, these factors support the hypothesis that chronic seizure activity induces a cardiac HCN2 channelopathy with associated conduction disturbances, independent of epilepsy aetiology. Ventricular HCN4 mRNA expression was also reduced, though only in animals with genetic epilepsy.[13]

Voltage-gated sodium channels represent another family of ion channels whose cardiac expression appears altered in epilepsy. One group noted increased $Na_v1.1$ (*Scn1a*) and decreased $Na_v1.5$ (*Scn5a*) mRNA expression in ventricular cardiomyocytes from epileptic rats >1 month after kainate-induced SE, yet protein levels increased for both channels.[14] To explain the discrepancy in $Na_v1.5$ changes, the authors postulated that decreased $Na_v1.5$ transcription may trigger a compensatory increase in $Na_v1.5$ channel stability on the plasma membrane. Notably, molecular changes were accompanied by a lengthening of the ventricular action potential consistent with clinical QTc prolongation, attributed to an increase in sustained late sodium current (I_{NaL}).[14] However, $Na_v1.5$ expression remained unaltered in i) whole hearts from post-SE rats at a later time-point,[16] and ii) ventricular myocytes from an animal model of Dravet syndrome expressing a human *SCN1A* mutation.[22] Therefore, cardiac dysregulation of voltage-gated sodium channels may depend on epilepsy aetiology or chronicity.

Seizure activity may also affect the expression of voltage-gated potassium channels in the heart. Whole heart myocardial $K_v4.2$ protein expression was decreased two weeks post-chemoconvulsant induction of SE in animals.[12,15] Moreover, this animal model of acquired epilepsy exhibited reductions in both whole heart cardiac $K_v4.2$ and $K_v4.3$ expression 7-18 months post-SE, a time period modelling established epilepsy.[16] Concurrent electrophysiological changes included higher heart rate, longer QRS duration, and slower myocardial conduction velocity. Additionally, there was evidence of abnormal ventricular repolarization, with greater susceptibility to ventricular arrhythmias and increased QTc length and variability.[12,15,16] These findings are consistent with a decrease in $K_v4.2$ and $K_v4.3$-

mediated transient outwards potassium current (I_{to}), which facilitates the early (phase I) repolarization of action potentials.

Concerning calcium-conducting ion channels, the same group found that whole heart expression of sodium-calcium exchanger-1 (NCX1) protein was decreased two weeks following kainate-induced SE. Altered calcium homeostasis was also apparent, consistent with an expected reduction in NCX1-mediated removal of intracellular calcium.[15] Importantly, the early two-week timepoint in post-SE animals falls during the latent phase, which precedes the development of recurrent spontaneous seizures.[15,23] Therefore, this result strictly demonstrates an NCX1 channelopathy following status epilepticus – a single convulsive event, rather than chronic epilepsy *per se*. Otherwise, there was no evidence of a change in whole heart L-type $Ca_v1.2$ expression 7-18 months after pilocarpine-induced SE.[16]

To date, studies have reported altered cardiac expression of i) HCN2 and HCN4; ii) $Na_v1.1$ and $Na_v1.5$; iii) $K_v4.2$ and $K_v4.3$; and iv) NCX1 channels in animals with epilepsy (Figure 1). However, published evidence of the same phenomena in humans is absent.

3.2 Potential relevance of inherited cardio-cerebral channelopathies

Inherited defects in ion channels which regulate both cardiac and neuronal excitability may generate a dual arrhythmia and seizure phenotype, representing a potential "cardio-cerebral channelopathy" (Table 1). Though mechanistically distinct from an acquired cardiac channelopathy (Figure 2) – whereby epilepsy secondarily alters cardiac ion channel expression, the same ion channels could be involved in both aetiologies. Significantly, the electrocardiographic QT prolongation seen in epilepsy constitutes the cardinal feature of long QT syndrome (LQTS) – which predisposes patients to *torsade de pointes* (a serious ventricular tachycardia). Indeed, over 90% of congenital LQTS mutations involve three ion channel genes – *KCNQ1, KCNH2,* and *SCN5A*.[24]

That a common channelopathy may disrupt electrical activity in both brain and heart is supported by several observations. Firstly, a retrospective study of 1901 LQTS cases noted a clinical overlap between epilepsy and arrhythmogenic syndromes. Patients with a confirmed genetic diagnosis of LQTS were three times more likely to have a seizure phenotype, while those suffering seizures were four times more likely to experience arrhythmias.[19] Secondly, genomic analysis of an epilepsy cohort found that nine out of 42 epilepsy patients harboured potentially pathogenic single nucleotide polymorphisms in LQTS genes, of which five suffered an arrhythmogenic syndrome as well.[18] Mutations in the four HCN genes (*HCN1-4*)

were also identified in 19% of cases from a SUDEP cohort.[25] Lastly, animal studies indicate that abnormal expression or function of some ion channels mediate a dual cardio-cerebral phenotype (Table 1, Supplementary Table 1). One example is mice harbouring *KCNQ1* mutations (coding for the $K_v7.1$ channel), which display frequent seizures and interictal epileptiform EEG discharges, as well as cardiac arrhythmias such as atrial fibrillation.[26]

Intriguingly, there appears to be an empirical overlap in the ion channels involved in both inherited cardio-cerebral channelopathies and acquired epilepsy-related cardiac channelopathies (comparing Figure 1 and Table 1) despite their aetiological distinction. For example, HCN2-deficient mice exhibit both absence seizures and sinus dysrhythmia,[21] and there is also evidence of an acquired HCN2 channelopathy in epilepsy.[13] Likewise, *SCN5A* mutations have been identified in patients suffering both epilepsy and LQTS,[27] while altered $Na_v1.5$ (*Scn5a*) mRNA and protein expression have also been observed in animals with acquired epilepsy.[14] Given this overlap, it is conceivable that ion channel genes linked to a dual cardio-cerebral phenotype might also undergo altered cardiac expression secondary to seizure activity.

4. Pathophysiology of altered cardiac ion channel expression in epilepsy

While the pathophysiology of an acquired cardiac channelopathy in epilepsy is poorly understood, autonomic dysfunction and structural cardiac disease represent key candidate mechanisms. This section will first establish how these mechanisms are known to occur in epilepsy (Sections 4.1 and 4.2), then explore ion channel dysregulation in comparable cardiac pathology independent of epilepsy (Section 4.3). Other possible factors are discussed in Section 4.4.

4.1 Autonomic dysfunction in epilepsy

Abnormal autonomic output to the heart may represent an important mediator of cardiac dysfunction in epilepsy. Tachycardic and hypertensive responses accompanied more than 25% of seizures in one video-EEG monitoring unit, though less common bradycardia and hypotension also occurred.[28] Indeed, analysis of heart rate variability during seizures revealed evidence of both increased sympathetic and decreased parasympathetic activity.[28] These ECG markers of autonomic dysfunction also persist interictally,[7] with greater severity among patients suffering refractory seizures.[29] Furthermore, prevention and reversal of QTc prolongation and arrhythmic susceptibility by adrenergic blockage highlights the role of seizure-related sympathetic overactivity in driving chronic cardiac dysfunction.[12,16]

At an intracellular level, animals with chronic epilepsy and an acquired cardiac channelopathy exhibit β1-adrenoceptor downregulation, $\alpha 1_A$-adrenoceptor upregulation and increased myocardial connexin-43 expression, indicating elevated sympathetic tone.[15,16] β1-adrenergic overactivity in the setting of epilepsy also coincided with induction of both classical cAMP/PKA (cyclic AMP/protein kinase A) signalling, and non-classical CaMKII (Ca^{2+}/calmodulin-dependent kinase II) and ERK1/2 (extracellular signal-regulated kinases 1/2) activation.[15] Moreover, experimental studies of cardiac development and disease have characterised a complex regulatory network governing ion channel gene transcription.[30] Critical developmental and global transcription factors within cardiomyocytes include Nkx2-5, GATA4, Tbx5, MEF2 and SRF - some of which are also activated by adrenergic agonists and protein kinases.[31,32] Therefore, overstimulation of autonomic pathways may mediate the transcriptional dysregulation of cardiac ion channels in epilepsy.

Despite cardiac evidence of autonomic dysfunction in epilepsy, the precise origin of this dysautonomia remains unclear. Seizure activity originating from or spreading to cortical (e.g. insula and pre-frontal cortex) and limbic (e.g. hypothalamus, amygdala, cingulate, and peri-aqueductal gray) regulators of brainstem autonomic output may be responsible.[3] These structures lie either within, or in proximity to the temporal lobe, which could explain why temporal seizures are associated with ictal tachycardia.[28] Accordingly, ECG markers of autonomic dysfunction during temporal seizures correlate with electrical activity in the hypothalamus and amygdala.[33] Clues have also arisen from imaging studies of patients with temporal lobe epilepsy, which revealed functional abnormalities in subcortical autonomic centres,[34] and altered post-ganglionic innervation of cardiac tissue by sympathetic fibres.[35]

4.2 Structural cardiac disease in epilepsy

Epilepsy is associated with evidence of mechanical dysfunction and structural abnormalities of the heart, which may underlie ion channel dysregulation in cardiomyocytes. Echocardiographic examination of newly diagnosed drug-naïve patients with generalized epilepsy found markers of both systolic dysfunction – e.g. decreased ejection fraction, and diastolic dysfunction – e.g. elevated left ventricular filling pressure.[10] Moreover, a recent study found increased cardiac stiffness among young patients suffering temporal lobe epilepsy without pre-existing cardiovascular disease. Regression analyses noted autonomic dysfunction to be responsible for more than 50% of this cardiac abnormality.[36] Furthermore, post-mortem examination has revealed irreversible perivascular and interstitial fibrosis of the

myocardium among cases of SUDEP, absent in healthy individuals who died of other causes.[37]

Animals with epilepsy exhibit similar features of structural cardiac disease, with evidence of an autonomic contribution. One group noted biochemical, pharmacological and electrical markers of sympathetic predominance in post-SE animals, which preceded histological signs of cardiomyocyte injury one month after SE.[9] Therefore, seizure-related sympathetic overstimulation may damage the myocardium and lead to maladaptive cardiac remodelling, with evidence of eccentric hypertrophy and a dilated cardiomyopathy secondary to epilepsy.[9] Indeed, invasive cardiac monitoring of rats suffering audiogenic seizures confirmed both systolic and diastolic dysfunction across the cardiac cycle.[11]

Significantly, the structural cardiac abnormalities observed in epilepsy are themselves independently associated with ion channel remodelling. For instance, failing hearts secondary to a dilated cardiomyopathy exhibit altered cardiac expression of various Na^+, K^+, Ca^{2+}, Cl^- and HCN channel genes compared with healthy hearts.[38] Thus, pathological cardiac remodelling may likewise mediate the acquired cardiac channelopathies seen in epilepsy.

4.3 Ion channel regulation in autonomic and structural cardiac dysfunction

The fact that epilepsy secondarily alters cardiac ion channel expression implies potential involvement of transcriptional pathways, distinct from post-translational modulation of ion channel function. The following discussion will focus on ion channel regulation in the context of primary cardiac pathology. Given the similarities between models of cardiac disease and epilepsy-related cardiac dysfunction, putative intracellular pathways which may mediate the acquired cardiac channelopathies seen in epilepsy are identified (see Figure 3).

4.3.1 Potassium channels

Primary cardiomyopathic changes alter the transcriptional regulation of voltage-gated potassium channels involved in both early ($K_v1.4/K_v4.2/K_v4.3$) and delayed ($K_v1.5/K_v7.1$) action potential repolarization.[39,40] Reductions in $K_v4.2$ and $K_v4.3$ expression have been demonstrated in heart failure and hypertrophy,[41,42] concordant with the cardiac $K_v4.2/K_v4.3$ downregulation noted in epilepsy.[16] Indeed, decreased K^+ channel expression appears conserved across animals with failing hearts secondary to i) dilated cardiomyopathy,[39] ii) angiotensin II-mediated hypertrophy,[42] iii) primary hypertension,[41] and iv) ventricular tachypacing,[40] – increasing the likelihood that an epilepsy-associated cardiac K^+

channelopathy is also mediated by structural dysfunction. Moreover, these animal models reflect the cardio-autonomic changes seen in epilepsy, including sympathetic overactivity, ventricular remodelling, and systolic and diastolic failure.[9,11]

Sympathetic signalling pathways also play an important role in regulating cardiac expression of voltage-gated potassium channels. One group found that β-adrenergic stimulation of cardiomyocytes reduced the expression of I_{to}-associated $K_v4.2$, $K_v4.3$ and KChIP2 (K^+ channel interacting protein 2) auxiliary subunit, mirroring the potassium channelopathy seen in animals with epilepsy.[43] Regarding the involvement of downstream pathways, CaMKII, calcineurin/NFAT and NF-κB signalling all differentially regulated $K_v4.2$, $K_v4.3$ and KChIP2 expression in non-stimulated baseline conditions. However, only NF-κB activation contributed to the downregulation of corresponding I_{to} current secondary to β-adrenergic stimulation.[43] Stimulation of α_1-adrenoceptors similarly decreased cardiac $K_v4.2$, $K_v4.3$ and KChIP2 levels, but downstream calcineurin/NFAT signalling alternatively increased $K_v4.2$ expression.[44] Following sympathetic induction of cAMP, cAMP-dependent CREB (cAMP response element binding protein) also upregulated $K_v4.2$ transcription and translation, further highlighting the presence of opposing regulatory pathways.[45] Additionally, both JAK-STAT signalling and angiotensin II induced downregulation of $K_v4.2$ post-myocardial infarction,[46] while angiotensin II and phenylephrine (α1-agonist) downregulated $K_v4.3$ expression.[47] Aside from adrenergic signalling, $K_v4.2$ expression was reduced by transcription factor Irx5,[48] while $K_v4.3$ expression was decreased by pro-inflammatory factor BMP-4 (bone morphogenic protein 4).[49]

4.3.2 Sodium channels

Primary cardiac pathology also alters the expression of voltage-gated sodium channels. One group found that pressure-overload heart failure reduced ventricular $Na_v1.5$ mRNA expression,[50] mirroring the molecular change seen in animals with acquired epilepsy.[14] The effect of cardiac remodelling on ion channel expression also varies between region, with increased ventricular but decreased sinoatrial node expression of $Na_v1.1$ and $Na_v1.6$ channels in heart failure.[50,51]

Several transcriptional factors may be involved, including GATA4 and Nkx2-5 – both important global regulators of cardiac development and cardiomyocyte proliferation.[30] Genetic analysis of cardiac tissue from heart failure patients demonstrated that *SCN5A* ($Na_v1.5$) transcription is directly activated by GATA4.[52,53] Mice lacking transcription factor

Nkx2-5 exhibit decreased ventricular $Na_v1.5$ expression alongside abnormal cardiac conduction and contraction.[54] Importantly, both GATA4 and Nkx2-5 were transactivated in mice with adrenergic-induced cardiac hypertrophy,[32] predicting a pathway that links cardiac dysautonomia and remodelling to altered sodium channel expression in epilepsy.

Recurrent myocardial ischaemia secondary to ictal sympathetic overactivity may also contribute the dysregulation of cardiac $Na_v1.5$ channels. Reactive oxygen species, which are released in oxidative stress, are known to recruit transcription factors Foxo1 and NF-κB to suppress *Scn5a* transcription.[55,56] This is in keeping with the decreased $Na_v1.5$ mRNA expression observed among post-SE animals modelling acquired epilepsy.[14] Additionally, transcription of the *Scn5a/Scn10a* locus is activated by Tbx5 and repressed by Tbx3 – members of the T-box family of transcription factors involved in cardiogenesis.[53]

4.3.3 Sodium-calcium exchangers

Both adrenergic stimulation and heart failure are associated with NCX1 overexpression *in vivo*, potentially representing a compensatory though maladaptive response aimed at increasing NCX1-mediated extrusion of excess calcium and preserving ventricular function. Chronic β-adrenoceptor stimulation of the adult murine heart upregulated NCX1 transcription in a CaMKII-dependent manner, with recruitment of ubiquitous AP-1 transcription factors (c-Jun and JunB) to NCX1 promoter regions.[57] β-adrenergic stimulation of cardiomyocytes also increased NCX1 expression via cAMP-PKA signalling,[57] while ERK1/2 signalling may play a role in α-adrenergic upregulation of NCX1.[58] In the setting of pressure overload-induced hypertrophy, both i) binding of histone deacetylases HDAC1/5 to Nkx2-5,[59] and ii) calcineurin activity,[60] acted as essential mediators of NCX1 overexpression. In contrast, myocardial NCX1 expression was decreased post-SE and associated with abnormal calcium homeostasis.[15] Though the transcriptional mediators are unclear, it is notable that Egr1 (early growth response protein 1) appears both responsive to adrenergic stimulation,[32] and negatively regulates cardiac NCX1 expression.[61] In addition, the transcriptional factor SRF (serum response factor) crucially regulates "fetal" cardiac genes including NCX1 during development, while GATA4 ensures cardiac-specific expression of NCX1.[62]

Given that NCX1 upregulation in heart failure is well-established,[63] the observed decrease in myocardial NCX1 expression following status epilepticus[15] argues against structural heart disease as a mediating factor in this channelopathy. In fact, altered cardiac expression of calcium-conducting channels may facilitate structural dysfunction, rather than vice versa.

Mice overexpressing NCX1 developed both cardiac hypertrophy and contractile impairment, proportional to NCX1 levels (homozygous > heterozygous).[64] These animals also showed a greater propensity to decompensate into heart failure following a period of haemodynamic stress. Mechanistically, the deleterious effects of NCX1 overexpression on contractile function were attributed to altered intracellular calcium transients and decreased sarcoplasmic calcium stores, consistent with the role of NCX1 in removing cytosolic calcium.[65] Indeed, NCX1 channels form part of the "fetal" cardiac gene program, whose abnormal re-expression is thought to underlie pathological cardiac remodelling.[62]

4.3.4 HCN channels

Comparatively fewer studies have examined the transcriptional regulators of HCN channels in cardiomyocytes. One group found that all four HCN genes contain recognition sequences for NRSF (neuron-restrictive silencing factor), which acts as a repressor of many neuronal genes.[66] Accordingly, transgenic mice expressing a dominant-negative NRSF mutation demonstrated cardiac overexpression of HCN2 and HCN4.[67] Therefore, NRSF activity may theoretically contribute to the downregulation of HCN2 (and possibly HCN4) channels in animals with acquired and genetic epilepsy. It is worth noting that HCN2 and HCN4 expression also exhibit regional variation, with increased ventricular expression in rats following myocardial infarction,[68] but decreased sinoatrial node expression in a canine model of tachypacing-induced heart failure.[69] Furthermore, HCN2 and HCN4 expression are i) transactivated by the ubiquitous Sp1 transcription factor in hypertrophic cardiomyocytes,[70] and ii) increased by aldosterone in neonatal ventricular myocytes.[71]

4.3.5 Calcium channels

There is no evidence that epilepsy secondarily alters the cardiac expression of L-type or T-type calcium channels. However, these channels are also involved in cardiac pacemaking, and their regulation appears likewise disrupted secondary to autonomic and structural dysfunction. In brief, Egr1 was found to mediate the overexpression of $Ca_v3.2$ (*Cacna1h*) T-type calcium channels in the setting of cardiomyocyte hypertrophy secondary to α_1-adrenergic stimulation.[72] Nkx2-5 overexpression also upregulated $Ca_v3.2$ mRNA levels,[73] while NRSF repressed ventricular $Ca_v3.2$ expression.[67] Additionally, cardiac expression of $Ca_v1.2$ (*Cacna1c*) was downregulated *in vitro* by i) overexpression of Nkx2-5 and GATA4 transcription factors,[73] and ii) CaMKII-mediated translocation of a downstream repressor complex.[74]

4.3.6 MicroRNAs

MicroRNAs (miR) have been increasingly recognized as important negative regulators of cardiac ion channel expression, and thus, may be involved in the molecular milieu underlying acquired cardiac channelopathies in epilepsy (Figure 3). MicroRNAs are small non-coding RNAs that either degrade target mRNAs or inhibit their translation into protein.[75] Specifically, miR-1 and miR-133 were found to repress the post-transcriptional expression of HCN2 and HCN4 in the setting of age-related atrial fibrillation and post-infarction heart failure.[68,76] Likewise, over-expression of miR-1 and miR-133 *in vitro* suppressed potassium channel $K_v7.1$ (*KCNQ1*) and its associated subunit (*KCNE1*). Cardiac investigation of mice lacking miR-1-2 (a member of the miR-1 family) also revealed $K_v4.2$ downregulation secondary to Irx5 overexpression, with abnormalities in cardiac morphogenesis, conduction, and myocyte cell cycling.[77] Furthermore, NCX1 expression was repressed by miR-1, which itself was modulated by transcriptional factor SRF and adrenergic stimulation.[78] Other microRNAs have also been implicated in cardiac ion channel regulation. These findings are summarised in Supplementary Table 2.

4.4 Other mechanisms

Epilepsy is associated with disruption of the blood-brain barrier and local release of inflammatory mediators such as interleukin (IL)-1β, IL-6 and tumor necrosis factor α (TNFα),[79] which may conceivably enter the circulation and affect myocardial ion channel expression. Indeed, it has been shown that TNFα downregulates the cardiac expression of $K_v4.2$ and $K_v4.3$ channels *in vitro*.[80] One group also screened IL-2 for transcriptional modulation of ion channel genes in myocardial cells, noting upregulation of *Scn3b* – a gene associated with Brugada syndrome and atrial fibrillation.[81] Another inflammatory factor, TGFβ1 (Transforming growth factor β1), increased *Scn5a* and decreased *Kcnd2* gene expression in murine ventricular myocytes.[82] However, studies have only demonstrated elevations in post-ictal plasma IL-6 and IL-8, along with increased interictal levels of plasma IL-6 in temporal lobe epilepsy.[83] Therefore, there is no indication that any specific cytokine is both i) systemically elevated in epilepsy, and ii) associated with cardiac ion channel dysregulation.

Furthermore, an exogenous contribution to cardiac ion channel remodelling from anti-epileptic drug (AED) therapy was considered. Only one study was identified, reporting upregulation of *Scn9a* and *Scn1b* gene expression with administration of valproate *in vitro*,

but this result has not been followed up.[84] In fact, the association between AED therapy and cardiac electrophysiology also remains unclear. While AED-treated epilepsy patients more frequently exhibit ST segment abnormalities compared with the general population, the effect of epilepsy itself could not be excluded as pre-medication ECGs were unavailable.[85] Moreover, a formal review failed to find conclusive evidence of an association between any specific AED and QTc prolongation, noting a lack of clinical data.[86]

4.5 Summary

The pathophysiology of altered cardiac ion channel expression in epilepsy may predominantly involve autonomic dysfunction and structural cardiac disease, as both mechanisms are independently associated with i) epilepsy, and ii) ion channel dysregulation. Specifically, epilepsy appears to alter autonomic output from the central nervous system, overstimulating sympathetic signalling pathways in cardiomyocytes. In parallel, seizure-related adrenergic overactivity may damage the myocardium, leading to a cardiomyopathy that may further elevate autonomic stimulation of the heart. Consequently, intracellular pathways are activated, altering the transcriptional regulation of ion channels (see Figure 4A). Evidence supporting a contribution from AED therapy or circulating inflammatory markers is lacking.

5. Clinical significance of altered cardiac ion channel expression in epilepsy

Clinically, perhaps the most pertinent question is whether an acquired cardiac channelopathy contributes to the elevated risk of sudden death in epilepsy. Figure 4B illustrates the hypothesis that altered cardiac ion channel expression chronically disrupts cardiac electrical function in epilepsy, rendering patients more susceptible to serious arrhythmias. Perhaps a two-hit model is involved – the first "hit" being a pre-existing electrophysiological vulnerability secondary to molecular remodelling, and the second "hit" being an acute seizure or cardiac stressor that triggers a life-threatening arrhythmic event.

Several factors indicate that altered cardiac ion channel expression may underlie conduction abnormalities in the setting of epilepsy. Firstly, molecular and electrophysiological abnormalities demonstrate functional concordance. Given that action potential repolarization is initiated by I_{to}-conducting $K_v4.x$ channels but opposed by I_{NaL}-conducting $Na_v1.x$ channels, a decrease in $K_v4.2/K_v4.3$ and increase in $Na_v1.1/Na_v1.5$ expression would expectedly lengthen the ventricular action potential, consistent with QTc prolongation.[12,14–16] Moreover, the ion channels implicated in an acquired cardiac

channelopathy secondary to epilepsy are, themselves, independently associated with abnormal cardiac electrophysiology. For example, deletion of cardiac HCN2 channels led to sinoatrial arrhythmias,[21] while functional knockout of $K_v4.2$ markedly prolonged action potentials and the QTc interval.[87]

The next step is to consider the relationship between epilepsy-related conduction abnormalities (e.g. QT interval changes) and cardiac mortality or SUDEP. QTc prolongation was independently associated with ventricular arrhythmia and sudden cardiac death in both healthy population-wide cohorts,[88] and patients with acquired long QT intervals, e.g. due to ischaemic heart disease, diabetes, or QT-prolonging drugs.[89] Similarly, QTc dispersion (variability) was found to incrementally increase the risk of sudden cardiac death.[90] Recently, one group showed that heart rate variability was decreased among cases of SUDEP versus individuals with epilepsy, indicating autonomic dysfunction.[8] This was consistent with earlier evidence of a correlation between SUDEP risk and lower RMSSD (Root Mean Square of Successive Differences) – reflecting depressed vagal modulation of heart rate variability.[91] However, other studies comparing suspected SUDEP cases with matched epilepsy controls revealed no difference in resting ECG measures nor heart rate variability.[92,93]

Elucidating the role of altered cardiac ion channel expression in SUDEP is complicated by uncertainties surrounding the circumstances of SUDEP itself. Firstly, it is difficult to ascertain the cardiac contribution to SUDEP events given their multifactorial pathophysiology. Cerebral compromise, hypoventilation, hypoxia, and brady and tachy-arrhythmias are all implicated.[1,94] Indeed, investigating the mechanism of death is limited by the extremely low likelihood of witnessing a SUDEP event with continuous cardiorespiratory monitoring. Even the fortuitous capture of SUDEP in animals with ion channel deletions or mutations reveal a distinct sequence of cerebro-cardio-respiratory features for each death.[26,95]

Secondly, whether the potentially fatal consequences of a pro-arrhythmic state manifest interictally or peri-ictally depends on whether SUDEP events occur during, or in the absence of seizures. Although some SUDEP cases have been witnessed without seizure activity,[96] many argue that SUDEP is almost exclusively seizure-related[97] given the lack of definitive EEG and clinical documentation to the contrary.[1] However, other evidence suggests that epilepsy itself is a risk factor for sudden cardiac death in the absence of peri-mortem seizure.[98] Therefore, cardiac and autonomic dysfunction may render epilepsy patients more vulnerable to fatal arrhythmias both during and between seizures.

Lastly, it is important to consider whether cardiac dysfunction in epilepsy is potentially preventable or reversible. Treatment with atenolol, a β1-selective antagonist, may prevent and/or reverse QTc prolongation and susceptibility to ventricular arrhythmias.[12,16] However, it is not known whether an epilepsy-related acquired cardiac channelopathy could similarly be modulated by pharmacological blockade of sympathetic activity, or perhaps reversed by AEDs in lieu of seizure reduction. Moreover, the prospect of prevention or reversal is limited by a lack of reliable and validated SUDEP biomarkers, without which one cannot identify high-risk epilepsy patients who might benefit from cardiac-directed therapy.[20,94]

6. Conclusions

Recent animal studies indicate that epilepsy secondarily alters the cardiac expression of sodium (Na_v), potassium (K_v), calcium (NCX), and cation-conducting (HCN) channels. Alongside ictal and interictal changes in autonomic, electrophysiological and dynamic cardiac function, a molecular cardiac channelopathy further highlights the complexity of brain-heart interactions in epilepsy. Clinical investigation is required to determine whether patients with epilepsy undergo similar remodelling of cardiac ion channel expression, given the possibility that such changes may underlie a pro-arrhythmic state. While there is evidence that sympathetic overactivity and myocardial remodelling facilitate transcriptional dysregulation of cardiac ion channels in epilepsy, the precise pathophysiology remains unknown. In this review, putative intracellular pathways were identified by synthesising findings from epilepsy studies and the cardiac literature. However, this approach is limited by the variable behaviour of intracellular mediators and transcription factors in homeostatic versus pathological environments, and in primary cardiac pathology (e.g. post-infarction or pressure-overload heart failure) versus cardiac dysfunction secondary to epilepsy.

The significance of future work in this area depends on establishing the extent to which an acquired cardiac channelopathy predicts or influences cardiac morbidity and mortality in the context of epilepsy. Specifically, it will be important to investigate the underlying neural, cellular, and transcriptional mechanisms involved. Perhaps a combination of intracellular pathways, and likewise a combination of different ion channels, additively or synergistically impairs cardiac function in patients with chronic epilepsy. Thus, the impetus may fall on isolating the mechanisms that are most clinically significant. Investigating pharmacological prevention of an acquired cardiac channelopathy in epilepsy will also be of interest but requires the pre-requisite establishment of robust SUDEP biomarkers to identify individuals

at risk. Future research in this area will hopefully improve our understanding of the pathophysiology and significance of epilepsy-related cardiac dysfunction, both in a molecular and clinical context.

KEY POINTS:

- Animal studies show that epilepsy alters the cardiac expression of sodium ($Na_v1.1/1.5$), potassium ($K_v4.2/4.3$), calcium (NCX1), and cationic (HCN2/4) channels
- An acquired cardiac channelopathy may partly facilitate the pro-arrhythmic state seen in epilepsy, contributing to the risk of sudden death
- Inherited ion channels mutations co-expressed in brain and heart highlight the relationship between epilepsy, cardiac dysfunction and molecular changes
- Although the underlying pathophysiology remains uncertain, epilepsy-related autonomic dysfunction and cardiac remodelling may play a predominant role
- Establishing the clinical significance of an acquired cardiac channelopathy in epilepsy is vital, given the implications for cardiac dysfunction and mortality

DISCLOSURE OF CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. The authors acknowledge support from the NHMRC Project Grant #APP1082215 and NHMRC Program Grant #APP1091593.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES:

1. Devinsky O. Sudden, unexpected death in epilepsy. N Engl J Med 2011; 365:1801–1811.
2. Harden C, Tomson T, Gloss D, et al. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2017; 88:1674–1680.
3. Ravindran K, Powell KL, Todaro M, et al. The pathophysiology of cardiac dysfunction in epilepsy. Epilepsy Res 2016; 127:19–29.
4. Moseley BD, Wirrell EC, Nickels K, et al. Electrocardiographic and oximetric changes during partial complex and generalized seizures. Epilepsy Res 2011; 95:237–245.
5. Zijlmans M, Flanagan D, Gotman J. Heart rate changes and ECG abnormalities during epileptic seizures: prevalence and definition of an objective clinical sign. Epilepsia 2002; 43:847–854.
6. Kishk NA, Sharaf Y, Ebraheim AM, et al. Interictal cardiac repolarization abnormalities in people with epilepsy. Epilepsy Behav 2018; 79:106–111.

7. Lotufo PA, Valiengo L, Benseñor IM, et al. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia 2012; 53:272–282.
8. Myers KA, Bello-Espinosa LE, Symonds JD, et al. Heart rate variability in epilepsy: A potential biomarker of sudden unexpected death in epilepsy risk. Epilepsia 2018; 59:1372–1380.
9. Read MI, McCann DM, Millen RN, et al. Progressive development of cardiomyopathy following altered autonomic activity in status epilepticus. Am J Physiol Heart Circ Physiol 2015; 309:H1554–64.
10. Bilgi M, Yerdelen D, Cölkesen Y, et al. Evaluation of left ventricular diastolic function by tissue Doppler imaging in patients with newly diagnosed and untreated primary generalized epilepsy. Seizure 2013; 22:537–541.
11. Fazan R, Silva CAA, Oliveira JAC, et al. Evaluation of cardiovascular risk factors in the wistar audiogenic rat (WAR) strain. PLoS ONE 2015; 10:e0129574.
12. Bealer SL, Little JG, Metcalf CS, et al. Autonomic and cellular mechanisms mediating detrimental cardiac effects of status epilepticus. Epilepsy Res 2010; 91:66–73.
13. Powell KL, Jones NC, Kennard JT, et al. HCN channelopathy and cardiac electrophysiologic dysfunction in genetic and acquired rat epilepsy models. Epilepsia 2014; 55:609–620.
14. Biet M, Morin N, Lessard-Beaudoin M, et al. Prolongation of action potential duration and QT interval during epilepsy linked to increased contribution of neuronal sodium channels to cardiac late Na+ current: potential mechanism for sudden death in epilepsy. Circ Arrhythm Electrophysiol 2015; 8:912–920.
15. Brewster AL, Marzec K, Hairston A, et al. Early cardiac electrographic and molecular remodeling in a model of status epilepticus and acquired epilepsy. Epilepsia 2016; 57:1907–1915.
16. Lai Y-C, Li N, Lawrence W, et al. Myocardial remodeling and susceptibility to ventricular tachycardia in a model of chronic epilepsy. Epilepsia Open 2018; 3:213–223.
17. Molina-Navarro MM, Roselló-Lletí E, Ortega A, et al. Differential gene expression of cardiac ion channels in human dilated cardiomyopathy. PLoS ONE 2013; 8:e79792.
18. Partemi S, Vidal MC, Striano P, et al. Genetic and forensic implications in epilepsy and cardiac arrhythmias: a case series. Int J Legal Med 2015; 129:495–504.
19. Auerbach DS, McNitt S, Gross RA, et al. Genetic biomarkers for the risk of seizures in long QT syndrome. Neurology 2016; 87:1660–1668.
20. Glasscock E. Genomic biomarkers of SUDEP in brain and heart. Epilepsy Behav 2014; 38:172–179.
21. Ludwig A, Budde T, Stieber J, et al. Absence epilepsy and sinus dysrhythmia in mice lacking the pacemaker channel HCN2. EMBO J 2003; 22:216–224.
22. Auerbach DS, Jones J, Clawson BC, et al. Altered cardiac electrophysiology and SUDEP in a model of Dravet syndrome. PLoS ONE 2013; 8:e77843.
23. Glien M, Brandt C, Potschka H, et al. Repeated low-dose treatment of rats with pilocarpine: low mortality but high proportion of rats developing epilepsy. Epilepsy Res 2001; 46:111–119.
24. Amin AS, Tan HL, Wilde AAM. Cardiac ion channels in health and disease. Heart Rhythm 2010; 7:117–126.
25. Tu E, Waterhouse L, Duflou J, et al. Genetic analysis of hyperpolarization-activated cyclic nucleotide-gated cation channels in sudden unexpected death in epilepsy cases. Brain Pathol 2011; 21:692–698.
26. Goldman AM, Glasscock E, Yoo J, et al. Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. Sci Transl Med 2009; 1:2ra6.
27. Heron SE, Hernandez M, Edwards C, et al. Neonatal seizures and long QT syndrome: a cardiocerebral channelopathy? Epilepsia 2010; 51:293–296.
28. Jaychandran R, Chaitanya G, Satishchandra P, et al. Monitoring peri-ictal changes in heart rate variability, oxygen saturation and blood pressure in epilepsy monitoring unit. Epilepsy Res 2016; 125:10–18.
29. Mukherjee S, Tripathi M, Chandra PS, et al. Cardiovascular autonomic functions in well-controlled and intractable partial epilepsies. Epilepsy Res 2009; 85:261–269.
30. McCulley DJ, Black BL. Transcription factor pathways and congenital heart disease. Curr Top Dev Biol 2012; 100:253–277.
31. Liang Q, Wiese RJ, Bueno OF, et al. The transcription factor GATA4 is activated by extracellular signal-regulated kinase 1- and 2-mediated phosphorylation of serine 105 in cardiomyocytes. Mol Cell Biol 2001; 21:7460–7469.
32. Saadane N, Alpert L, Chalifour LE. Expression of immediate early genes, GATA-4, and Nkx-2.5 in adrenergic-induced cardiac hypertrophy and during regression in adult mice. Br J Pharmacol 1999; 127:1165–1176.

33. Chouchou F, Bouet R, Pichot V, et al. The neural bases of ictal tachycardia in temporal lobe seizures. Clin Neurophysiol 2017; 128:1810–1819.
34. Allen LA, Harper RM, Kumar R, et al. Dysfunctional Brain Networking among Autonomic Regulatory Structures in Temporal Lobe Epilepsy Patients at High Risk of Sudden Unexpected Death in Epilepsy. Front Neurol 2017; 8:544.
35. Druschky A, Hilz MJ, Hopp P, et al. Interictal cardiac autonomic dysfunction in temporal lobe epilepsy demonstrated by [(123)I]metaiodobenzylguanidine-SPECT. Brain 2001; 124:2372–2382.
36. Fialho GL, Wolf P, Walz R, et al. Increased cardiac stiffness is associated with autonomic dysfunction in patients with temporal lobe epilepsy. Epilepsia 2018; 59:e85–e90.
37. Natelson BH, Suarez RV, Terrence CF, et al. Patients with epilepsy who die suddenly have cardiac disease. Arch Neurol 1998; 55:857–860.
38. Ortega A, Tarazón E, Roselló-Lletí E, et al. Patients with Dilated Cardiomyopathy and Sustained Monomorphic Ventricular Tachycardia Show Up-Regulation of KCNN3 and KCNJ2 Genes and CACNG8-Linked Left Ventricular Dysfunction. PLoS ONE 2015; 10:e0145518.
39. Suzuki T, Shioya T, Murayama T, et al. Multistep ion channel remodeling and lethal arrhythmia precede heart failure in a mouse model of inherited dilated cardiomyopathy. PLoS ONE 2012; 7:e35353.
40. Tsuji Y, Zicha S, Qi X-Y, et al. Potassium channel subunit remodeling in rabbits exposed to long-term bradycardia or tachycardia: discrete arrhythmogenic consequences related to differential delayed-rectifier changes. Circulation 2006; 113:345–355.
41. Goltz D, Schultz J-H, Stucke C, et al. Diminished Kv4.2/3 but not KChIP2 levels reduce the cardiac transient outward K+ current in spontaneously hypertensive rats. Cardiovasc Res 2007; 74:85–95.
42. Tozakidou M, Goltz D, Hagenström T, et al. Molecular and functional remodeling of I(to) by angiotensin II in the mouse left ventricle. J Mol Cell Cardiol 2010; 48:140–151.
43. Panama BK, Korogyi AS, Aschar-Sobbi R, et al. Reductions in the Cardiac Transient Outward K+ Current Ito Caused by Chronic β-Adrenergic Receptor Stimulation Are Partly Rescued by Inhibition of Nuclear Factor κB. J Biol Chem 2016; 291:4156–4165.
44. Gong N, Bodi I, Zobel C, et al. Calcineurin increases cardiac transient outward K+ currents via transcriptional up-regulation of Kv4.2 channel subunits. J Biol Chem 2006; 281:38498–38506.
45. Schulte JS, Seidl MD, Nunes F, et al. CREB critically regulates action potential shape and duration in the adult mouse ventricle. Am J Physiol Heart Circ Physiol 2012; 302:H1998–2007.
46. El-Adawi H, Deng L, Tramontano A, et al. The functional role of the JAK-STAT pathway in post-infarction remodeling. Cardiovasc Res 2003; 57:129–138.
47. Zhang TT, Takimoto K, Stewart AF, et al. Independent regulation of cardiac Kv4.3 potassium channel expression by angiotensin II and phenylephrine. Circ Res 2001; 88:476–482.
48. Costantini DL, Arruda EP, Agarwal P, et al. The homeodomain transcription factor Irx5 establishes the mouse cardiac ventricular repolarization gradient. Cell 2005; 123:347–358.
49. Sun B, Sheng Y, Huo R, et al. Bone morphogenetic protein-4 contributes to the down-regulation of Kv4.3 K+ channels in pathological cardiac hypertrophy. Biochem Biophys Res Commun 2013; 436:591–594.
50. Xi Y, Wu G, Yang L, et al. Increased late sodium currents are related to transcription of neuronal isoforms in a pressure-overload model. Eur J Heart Fail 2009; 11:749–757.
51. Du Y, Huang X, Wang T, et al. Downregulation of neuronal sodium channel subunits Nav1.1 and Nav1.6 in the sinoatrial node from volume-overloaded heart failure rat. Pflugers Arch 2007; 454:451–459.
52. Tarradas A, Pinsach-Abuin ML, Mackintosh C, et al. Transcriptional regulation of the sodium channel gene (SCN5A) by GATA4 in human heart. J Mol Cell Cardiol 2017; 102:74–82.
53. Van den Boogaard M, Wong LYE, Tessadori F, et al. Genetic variation in T-box binding element functionally affects SCN5A/SCN10A enhancer. J Clin Invest 2012; 122:2519–2530.
54. Briggs LE, Takeda M, Cuadra AE, et al. Perinatal loss of Nkx2-5 results in rapid conduction and contraction defects. Circ Res 2008; 103:580–590.
55. Mao W, You T, Ye B, et al. Reactive oxygen species suppress cardiac NaV1.5 expression through Foxo1. PLoS ONE 2012; 7:e32738.
56. Shang LL, Sanyal S, Pfahnl AE, et al. NF-kappaB-dependent transcriptional regulation of the cardiac scn5a sodium channel by angiotensin II. Am J Physiol, Cell Physiol 2008; 294:C372–9.

57. Mani SK, Egan EA, Addy BK, et al. beta-Adrenergic receptor stimulated Ncx1 upregulation is mediated via a CaMKII/AP-1 signaling pathway in adult cardiomyocytes. J Mol Cell Cardiol 2010; 48:342–351.
58. Menick DR, Xu L, Kappler C, et al. Pathways regulating Na+/Ca2+ exchanger expression in the heart. Ann N Y Acad Sci 2002; 976:237–247.
59. Harris LG, Wang SH, Mani SK, et al. Evidence for a non-canonical role of HDAC5 in regulation of the cardiac Ncx1 and Bnp genes. Nucleic Acids Res 2016; 44:3610–3617.
60. Wang Z, Nolan B, Kutschke W, et al. Na+-Ca2+ exchanger remodeling in pressure overload cardiac hypertrophy. J Biol Chem 2001; 276:17706–17711.
61. Wang C, Dostanic S, Servant N, et al. Egr-1 negatively regulates expression of the sodium-calcium exchanger-1 in cardiomyocytes in vitro and in vivo. Cardiovasc Res 2005; 65:187–194.
62. Xu L, Renaud L, Müller JG, et al. Regulation of Ncx1 expression. Identification of regulatory elements mediating cardiac-specific expression and up-regulation. J Biol Chem 2006; 281:34430–34440.
63. Studer R, Reinecke H, Bilger J, et al. Gene expression of the cardiac Na(+)-Ca2+ exchanger in end-stage human heart failure. Circ Res 1994; 75:443–453.
64. Roos KP, Jordan MC, Fishbein MC, et al. Hypertrophy and heart failure in mice overexpressing the cardiac sodium-calcium exchanger. J Card Fail 2007; 13:318–329.
65. Pogwizd SM, Bers DM. Na/Ca exchange in heart failure: contractile dysfunction and arrhythmogenesis. Ann N Y Acad Sci 2002; 976:454–465.
66. Johnson DS, Mortazavi A, Myers RM, et al. Genome-wide mapping of in vivo protein-DNA interactions. Science 2007; 316:1497–1502.
67. Kuwahara K, Saito Y, Takano M, et al. NRSF regulates the fetal cardiac gene program and maintains normal cardiac structure and function. EMBO J 2003; 22:6310–6321.
68. Suffredini S, Stillitano F, Comini L, et al. Long-term treatment with ivabradine in post-myocardial infarcted rats counteracts f-channel overexpression. Br J Pharmacol 2012; 165:1457–1466.
69. Zicha S, Fernández-Velasco M, Lonardo G, et al. Sinus node dysfunction and hyperpolarization-activated (HCN) channel subunit remodeling in a canine heart failure model. Cardiovasc Res 2005; 66:472–481.
70. Lin H, Xiao J, Luo X, et al. Transcriptional control of pacemaker channel genes HCN2 and HCN4 by Sp1 and implications in re-expression of these genes in hypertrophied myocytes. Cell Physiol Biochem 2009; 23:317–326.
71. Muto T, Ueda N, Opthof T, et al. Aldosterone modulates I(f) current through gene expression in cultured neonatal rat ventricular myocytes. Am J Physiol Heart Circ Physiol 2007; 293:H2710–8.
72. Hsu S-C, Chang Y-T, Chen C-C. Early growth response 1 is an early signal inducing Cav3.2 T-type calcium channels during cardiac hypertrophy. Cardiovasc Res 2013; 100:222–230.
73. Wang Y, Morishima M, Zheng M, et al. Transcription factors Csx/Nkx2.5 and GATA4 distinctly regulate expression of Ca2+ channels in neonatal rat heart. J Mol Cell Cardiol 2007; 42:1045–1053.
74. Ronkainen JJ, Hänninen SL, Korhonen T, et al. Ca2+-calmodulin-dependent protein kinase II represses cardiac transcription of the L-type calcium channel alpha(1C)-subunit gene (Cacna1c) by DREAM translocation. J Physiol (Lond) 2011; 589:2669–2686.
75. Kim GH. MicroRNA regulation of cardiac conduction and arrhythmias. Transl Res 2013; 161:381–392.
76. Li Y-D, Hong Y-F, Yusufuaji Y, et al. Altered expression of hyperpolarization-activated cyclic nucleotide-gated channels and microRNA-1 and -133 in patients with age-associated atrial fibrillation. Mol Med Report 2015; 12:3243–3248.
77. Zhao Y, Ransom JF, Li A, et al. Dysregulation of cardiogenesis, cardiac conduction, and cell cycle in mice lacking miRNA-1-2. Cell 2007; 129:303–317.
78. Tritsch E, Mallat Y, Lefebvre F, et al. An SRF/miR-1 axis regulates NCX1 and annexin A5 protein levels in the normal and failing heart. Cardiovasc Res 2013; 98:372–380.
79. Vezzani A, French J, Bartfai T, et al. The role of inflammation in epilepsy. Nat Rev Neurol 2011; 7:31–40.
80. Petkova-Kirova PS, Gursoy E, Mehdi H, et al. Electrical remodeling of cardiac myocytes from mice with heart failure due to the overexpression of tumor necrosis factor-alpha. Am J Physiol Heart Circ Physiol 2006; 290:H2098–107.
81. Zhao Y, Sun Q, Zeng Z, et al. Regulation of SCN3B/scn3b by Interleukin 2 (IL-2): IL-2 modulates SCN3B/scn3b transcript expression and increases sodium current in myocardial cells. BMC Cardiovasc Disord 2016; 16:1.
82. Kaur K, Zarzoso M, Ponce-Balbuena D, et al. TGF-β1, released by myofibroblasts, differentially regulates transcription and function of sodium and potassium channels in adult rat ventricular myocytes. PLoS ONE 2013; 8:e55391.

83. Li G, Bauer S, Nowak M, et al. Cytokines and epilepsy. Seizure 2011; 20:249–256.
84. Yamamoto R, Yanagita T, Kobayashi H, et al. Up-regulation of sodium channel subunit mRNAs and their cell surface expression by antiepileptic valproic acid: activation of calcium channel and catecholamine secretion in adrenal chromaffin cells. J Neurochem 1997; 68:1655–1662.
85. Ishizue N, Niwano S, Saito M, et al. Polytherapy with sodium channel-blocking antiepileptic drugs is associated with arrhythmogenic ST-T abnormality in patients with epilepsy. Seizure 2016; 40:81–87.
86. Feldman AE, Gidal BE. QTc prolongation by antiepileptic drugs and the risk of torsade de pointes in patients with epilepsy. Epilepsy Behav 2013; 26:421–426.
87. Barry DM, Xu H, Schuessler RB, et al. Functional knockout of the transient outward current, long-QT syndrome, and cardiac remodeling in mice expressing a dominant-negative Kv4 alpha subunit. Circ Res 1998; 83:560–567.
88. Straus SMJM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. J Am Coll Cardiol 2006; 47:362–367.
89. Elming H, Brendorp B, Køber L, et al. QTc interval in the assessment of cardiac risk. Card Electrophysiol Rev 2002; 6:289–294.
90. De Bruyne MC, Hoes AW, Kors JA, et al. QTc dispersion predicts cardiac mortality in the elderly: the Rotterdam Study. Circulation 1998; 97:467–472.
91. DeGiorgio CM, Miller P, Meymandi S, et al. RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: the SUDEP-7 Inventory. Epilepsy Behav 2010; 19:78–81.
92. Chyou JY, Friedman D, Cerrone M, et al. Electrocardiographic features of sudden unexpected death in epilepsy. Epilepsia 2016; 57:e135–9.
93. Surges R, Henneberger C, Adjei P, et al. Do alterations in inter-ictal heart rate variability predict sudden unexpected death in epilepsy? Epilepsy Res 2009; 87:277–280.
94. Tomson T, Surges R, Delamont R, et al. Who to target in sudden unexpected death in epilepsy prevention and how? Risk factors, biomarkers, and intervention study designs. Epilepsia 2016; 57 Suppl 1:4–16.
95. Glasscock E, Yoo JW, Chen TT, et al. Kv1.1 potassium channel deficiency reveals brain-driven cardiac dysfunction as a candidate mechanism for sudden unexplained death in epilepsy. J Neurosci 2010; 30:5167–5175.
96. Kloster R, Engelskjøn T. Sudden unexpected death in epilepsy (SUDEP): a clinical perspective and a search for risk factors. J Neurol Neurosurg Psychiatr 1999; 67:439–444.
97. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology 2005; 64:1131–1133.
98. Bardai A, Lamberts RJ, Blom MT, et al. Epilepsy is a risk factor for sudden cardiac arrest in the general population. PLoS ONE 2012; 7:e42749.

Supporting Information:

Supplementary Table 1: Ion channels associated with both aberrant neuronal and cardiac excitability phenotypes (with reference list)

Supplementary Table 2: MicroRNAs that regulate cardiac cell surface ion channels (with reference list)

Figure legends:

Figure 1: Evidence of altered cardiac ion channel expression secondary to epilepsy in animals. Animals with acquired epilepsy following chemo-convulsant induction of status epilepticus exhibit altered cardiac mRNA and protein expression of HCN2, K_v4.2, K_v4.3, NCX1, Na_v1.1, and Na_v1.5.[12–16] Animal models of genetic epilepsy exhibit altered cardiac mRNA and protein expression of HCN2,[13] altered mRNA expression of HCN4 (in ventricles only),[13] but no change in Na_v1.5 channels.[22]

Figure 2: Schematic representation of the aetiological difference between inherited and acquired channelopathies. (A) An acquired cardiac channelopathy secondary to epilepsy – epilepsy secondarily alters the gene and protein expression of cardiac ion channels, in association with pro-arrhythmic abnormalities in cardiac conduction. **(B)** An inherited cardio-cerebral channelopathy – inherited mutations in ion channels expressed in brain and heart generate a dual seizure and arrhythmia phenotype.

Figure 3: Possible intracellular pathways mediating an acquired cardiac channelopathy in epilepsy. Altered transcription and/or translation of K_v4.2, K_v4.3, Na_v1.1, Na_v1.5, NCX1, HCN2 and HCN4 has been demonstrated in cardiac tissue from animal models of epilepsy. Chronic epilepsy leads to sympathetic overactivity and structural cardiac remodelling, which may activate several downstream signalling pathways and mediators including cAMP/PKA, CaMKII, ERK1/2, and calcineurin/NFAT. In turn, activation of cardiac transcription factors such as GATA4 and Nkx2-5 may mediate the upregulation or downregulation of target ion channel genes. MicroRNAs (miR) also inhibit the translation of ion channel mRNA into protein. (Forward arrow represents upregulation, transverse arrow represents downregulation, circular arrow represents differential regulation depending on isoform, and dotted lines represent abbreviated pathways.)

Figure 4: Schematic representation of the potential pathophysiology and significance of altered cardiac ion channel expression in epilepsy. (A) In chronic epilepsy, abnormal autonomic output to the heart may increase adrenergic signalling in cardiomyocytes and damage the myocardium, leading to cardiac remodelling. Consequently, modulation of downstream effectors and transcription factors may differentially regulate cardiac ion channel expression. **(B)** An acquired cardiac channelopathy may underlie the abnormal electrocardiographic parameters and conduction disturbances seen in epilepsy. These

interictal changes are thought to induce a pro-arrhythmic state, in which a subsequent insult such as a seizure may trigger a terminal event.

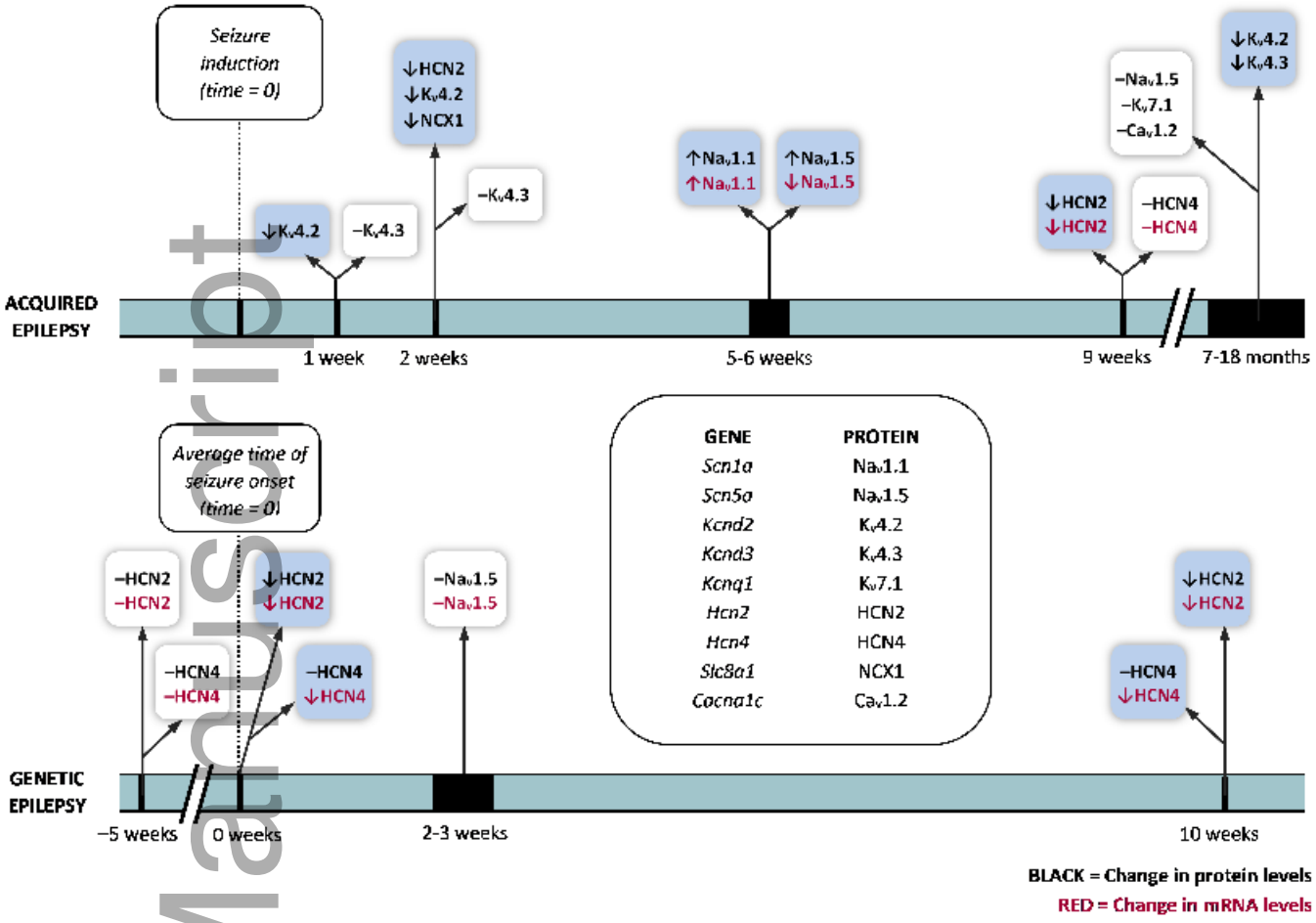
Table 1: Ion channels associated with both aberrant neuronal and cardiac excitability phenotypes[a]

Family	Gene	Protein	Function	Association with epilepsy	Association with arrhythmias
Voltage-gated sodium channels	SCN1A	$Na_v1.1$	Conducts fast depolarizing inwards Na^+ current for AP generation and propagation	Dravet syndrome and SUDEP; GEFS+	Cardiogenic paroxysmal SVT
	SCN1B	Na_v subunit β1	Interacts with $Na_v1.5$ to modulate its function and surface expression	Dravet syndrome; GEFS+	Brugada syndrome type 5; Susceptibility to polymorphic VT
	SCN5A	$Na_v1.5$	Conducts fast depolarizing inwards Na^+ current, and sustained/late sodium current	Generalized epilepsy; Neonatal seizures; SUDEP	LQTS type 3; Brugada syndrome type 1
	SCN8A	$Na_v1.6$	Conducts depolarizing inwards Na^+ current	Early infantile epileptic encephalopathy	Bradycardia and catecholamine-induced ventricular arrhythmias
	SCN10A	$Na_v1.8$	Conducts depolarizing inwards Na^+ current	LGS, infantile spasms and refractory seizures	Brugada syndrome
Voltage-gated potassium channels	KCNA1	$K_v1.1$	Conducts repolarizing outwards K^+ current	SUDEP; Focal epilepsy with episodic ataxia	Frequent AV blocks, prolonged bradycardias and excessive PVCs
	KCNE2	K_v subfamily E regulatory subunit 2	Interacts and co-assembles with $K_v11.1$ (and $K_v4.3$)	Generalized epilepsy; Neonatal seizures	LQTS type 6; Familial AF; Brugada ECG pattern
	KCNH2 (hERG)	$K_v11.1$	Conducts rapidly-activating delayed outward rectifying K^+ current for repolarization	Generalized epilepsy; Focal epilepsy	LQTS type 2; SQTS type 1
	KCNJ2	Kir2.1	Conducts inward rectifying K^+ current for repolarization and RMP stabilization	Autism-epilepsy phenotype	Familial AF; SQTS type 3; LQTS type 7 (Andersen-Tawil syndrome)
	KCNQ1	$K_v7.1$	Conducts slowly-activating delayed outward rectifying K^+ current for depolarization	Focal and generalized seizures; Interictal EEG discharges; SUDEP	LQTS type 1; SQTS type 2; Familial AF
Voltage-gated calcium channels	CACNA1C	$Ca_v1.2$	Conducts L-type inwards Ca^{2+} current responsible for AP plateau and intracellular Ca^{2+} transients	Neonatal onset epileptic encephalopathy; Late-onset epilepsy	Brugada syndrome type 3; LQTS type 8 (Timothy syndrome)
	CACNA1G	$Ca_v3.1$	Conducts T-type inwards Ca^{2+} responsible for pacemaking	Juvenile myoclonic epilepsy	Bradycardia, slowed sinoatrial pacemaking and slowed AV conduction
HCN channels	HCN2	HCN2	Conducts an inwards depolarizing Na^+/K^+ current in response to hyper-polarization for pacemaking	Absence epilepsy	Sinoatrial dysrhythmia
Other channels	RYR2	Ryanodine receptor 2	Enables Ca^{2+} release from the sarcoplasmic reticulum for excitation-contraction coupling in cardiomyocytes	Epileptiform EEG activity; Generalized seizures	CPVT; Exercise-induced ventricular arrhythmia and sudden cardiac death

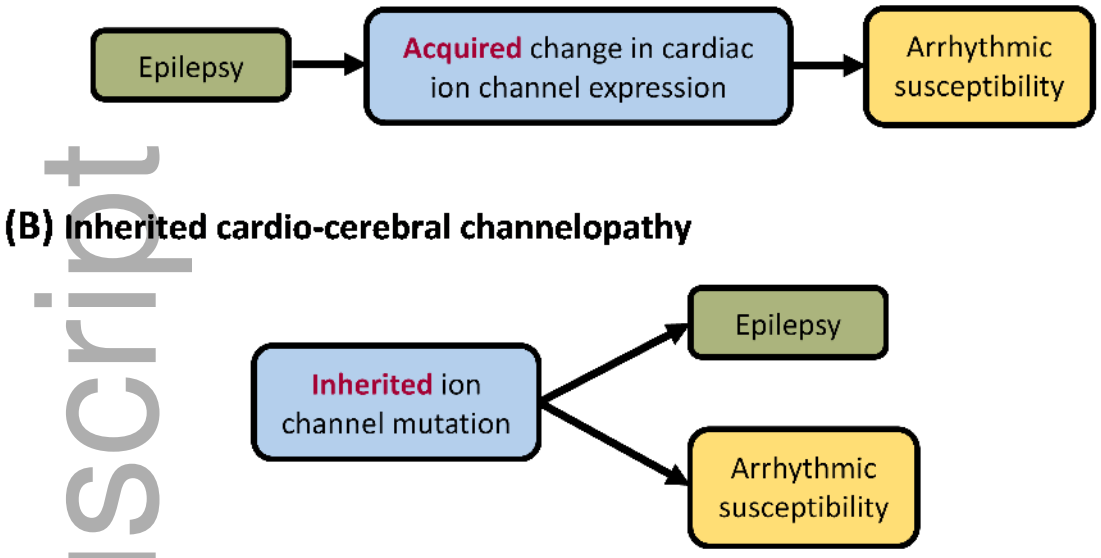
AP (action potential); SVT (supraventricular tachycardia), SE (status epilepticus), SUDEP (sudden unexpected death in epilepsy), GEFS+ (generalized epilepsy with febrile seizures plus), VT (ventricular tachycardia), GTCS (generalized tonic-clonic seizure), LQTS (long QT syndrome), LGS (Lennox-Gastaut syndrome), TLE (temporal lobe epilepsy), AV

(atrioventricular), PVC (premature ventricular contraction), AF (atrial fibrillation), SQTS (short QT syndrome), CPVT (catecholaminergic polymorphic ventricular tachycardia).

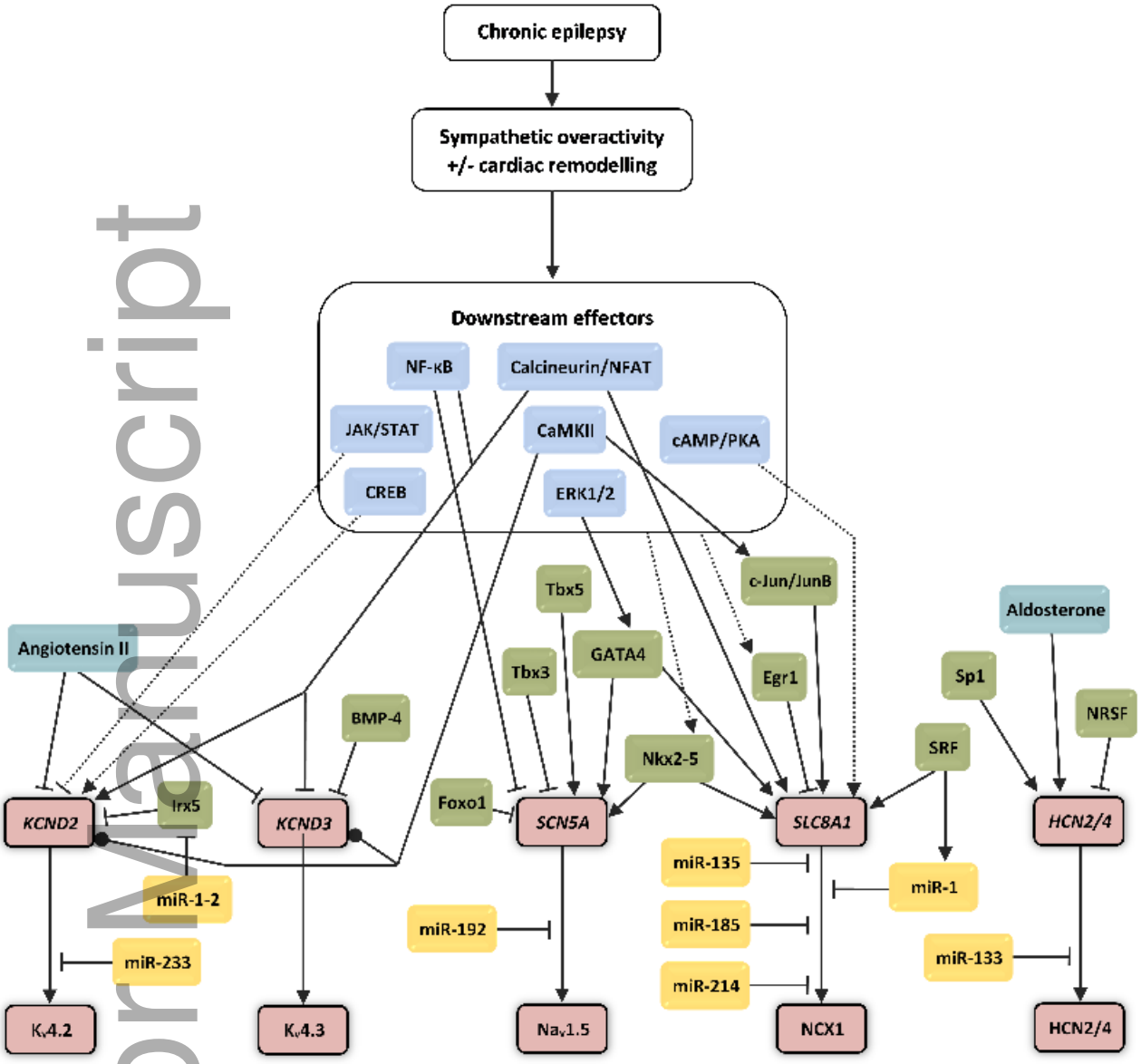
[a] See Supplementary Table 1 for relevant references.



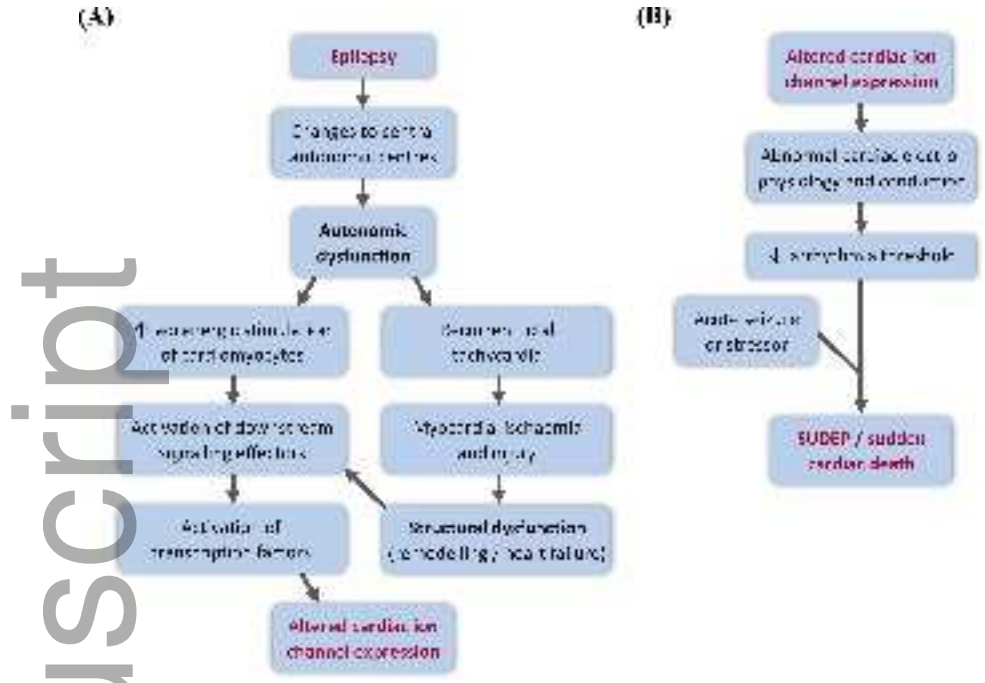
epi_16301_f1.tif



epi_16301_f2.tif



epi_16301_f3.tif



epi_16301_f4.tif