

Editorial – Channelopathies: a link between brain and heart: the model of epilepsy

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Channelopathies are a various set of disorders characterized by the dysfunction of ion channels in the membranes of all cells and many cellular organelles. Many pediatric diseases of the nervous system (e.g., generalized epilepsy with febrile seizures plus, familial hemiplegic migraine, episodic ataxia, and hyperkalemic and hypokalemic periodic paralysis) can be caused by channelopathies. Moreover, also diseases of the cardiovascular system (e.g., long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia), of the respiratory system (e.g., cystic fibrosis), of the endocrine system (e.g., neonatal diabetes mellitus, familial hyperinsulinemic hypoglycemia, thyrotoxic hypokalemic periodic paralysis, and familial hyperaldosteronism), of the urinary system (e.g., Bartter syndrome, nephrogenic diabetes insipidus, autosomal-dominant polycystic kidney disease, and hypomagnesemia with secondary hypocalcemia), and of the immune system (e.g., myasthenia gravis, neuromyelitis optica, Isaacs' syndrome, and anti-NMDA [N-methyl-D-aspartate] receptor encephalitis) can be a consequence of a malfunction of the ion channel¹. Transient Receptor Potential (TRP) channel proteins are another family of proteins that are expressed in many tissues and cell types. TRP channels respond to different stimuli, including light, mechanical or chemical stimuli, temperature, pH or osmolarity². Recent studies showed that TRP channel dysfunction significantly contributes to the pathophysiology of cardiovascular, neurological, metabolic or neoplastic disorders³.

Ion channels play a pivotal role in generating membrane potential and function in several cellular activities, such as signal transduction, neurotransmitter release, muscle contraction, hormone secretion, hydro electrolyte balance, growth, motility, and apoptosis. Ion channels are classified according to the types of ions passing through them, the factors of their gating, their tissue expression patterns, and their structural characteristics. Ion channels can be in one of the following states: open, inactivated closed (refractory period), and resting closed. The gating (opening and closing) of ion channels is controlled by membrane potential (voltage), ligands (e.g., hormones and neurotransmitters), second messengers (e.g., calcium and cyclic nucleotides), light, temperature, and mechanical changes. Ion channels can be formed from a single protein (e.g., cystic fibrosis transmembrane conductance regulator, a chloride channel). Otherwise, ion channels can be formed from an assembly of several subunits, each a protein encoded by a different gene. More than 600 ion channel genes have been identified.

Congenital cardiac and cerebral channelopathies are the consequence of mutations in different genes encoding for sodium (Na), potassium (K) and calcium (Ca) voltage-gated channels. In principle, Na⁺ channels are involved in cardiac channelopathies, whilst K⁺ and Ca⁺ channels appear to be responsible for seizures and other neuromuscular disorders. Nevertheless, the increasing reports of patients/families presenting with epilepsy and cardiac arrhythmias and a unique mutation in one of the channel genes suggest a strict correlation between the two phenotypes.

Cardiac action potentials are generated from a delicate balance of several ionic currents. When there is a derangement in the function of the ion channel, life-threatening cardiac arrhythmias may occur when this equilibrium is impaired by ion channel derangement. Cardiac channelopathies are responsible for about half the sudden arrhythmic death syndrome cases and, at least, one out of five sudden infant death syndrome cases. Mutations in calcium, sodium, potassium, and TRP channel

genes have been identified to cause a variety of cardiac arrhythmia disorders, and polymorphisms have been suggested to be risk factors.

Congenital long QT syndrome (LQTS) can predispose to a high risk of ventricular tachyarrhythmias (e.g., torsade de pointes) and syncope; moreover, sudden cardiac death is the first genetically identified cardiac disorder due to cardiac channelopathy. To date, 13 types of LQTS have been linked to mutations in genes encoding ion channels or associated proteins. Loss-of-function mutations of potassium channel genes (KCNQ1, KCNH2, KCNE1, KCNE2, KCNJ2, and KCNJ5) in LQTS reduce the repolarizing currents (IKr, IKs, and IKir) required to conclude the cardiac action potential, leading to a prolongation of the QT interval. Gain-of-function mutations in calcium channel (CACNA1C) and sodium channel genes (SCN5A and SCN4B) in LQTS cause delayed channel closing and inactivation, with a resultant increased QT interval. On the contrary, loss-of-function mutations in calcium channel genes (CACNA1C, CACNB2, and CACNA2D1) enhance repolarization, resulting in shortening of the cardiac action potential in short QT syndrome. Loss-of-function mutations in sodium channel genes have been identified to cause Brugada syndrome, familial atrial fibrillation, sick sinus syndrome, familial heart block, and atrial standstill. It's interesting that both gain-of-function mutations (which decrease action potential duration) and loss-of-function mutations (which increase action potential duration) in potassium channel genes predispose to atrial fibrillation⁴.

Several disorders of nervous system, including epilepsies, can be a consequence of an alteration of neuronal signaling caused by channelopathies; so a derangement of Ion channels function are fundamental in their pathogenesis⁵.

Recently was highlighted that mutations in genes encoding voltage-gated sodium channels are correlated with epilepsy, cardiac conduction defects, skeletal muscle channelopathies and peripheral pain disorders⁶. Over 1300 sodium channel mutations in central and peripheral nervous system, heart and muscle are present. Some of these channelopathies can increase cortical excitability and cause severe epilepsy. For this reason, the use of verapamil (a L-type calcium channel antagonist) can be useful in some patients with drug-resistant epilepsy⁷.

Moreover, has been reported⁸ that astroglia and microglia, cell non-conventionally considered excitable with a defined function in nutrition, myelination, and phagocytosis may express sodium channel in both physiological and pathological conditions. These channels contribute to multiple functional roles that are probably unrelated to the generation of action potentials. There is growing evidence that these channels regulate or participate in effector functions of glia through signaling mechanisms that are just beginning to be understood. The regulation of glial function by sodium channels has particular implications for the response of reactive glia to central nervous system diseases and insults.

In drug-resistant epilepsy often there are alterations in cardiac electrophysiology. Chronic epilepsy can accompany with abnormalities in both sinoatrial node pacemaker current as well as ventricular repolarizing current; this can improve the risk of developing life-threatening cardiac arrhythmias. The onset of cardiac arrhythmias in drug-resistant epilepsy can be a key mechanism underlying the phenomenon of Sudden Unexpected Death in Epilepsy (SUDEP). The occurrence rate of sudden death in patients with epilepsy is estimated to be 1/1000 patients. Several studies examining both animal models and human patients have documented that chronic epilepsy can detrimentally affect cardiac function, the detailed pathophysiology remains unclear. Recent work has shown the expression of several key cardiac ion channels to be altered in animal models of genetic and acquired epilepsies. This has led to believe that cardiac ion channel expression may be altered as a consequence of seizure activity. Furthermore, cortical autonomic dysfunction – resulting from seizure activity – has also been suggested to play an important role, while seizure activity may indirectly influence cardiac function via altering centrally-mediated autonomic output to the heart⁹.

Sudden loss of consciousness can be caused by syncope or epileptic seizure, which therefore requires a diagnostic work-up including cardiological and neurological examinations. Thus, in clinical practice cooperation of these two medical specialties is common and of high relevance. Seizures may lead to cardiac arrhythmia or ictal asystole, and SUDEP is an important field of epilepsy research. Cardiac channelopathies, such as long QT syndrome, may be associated with seizures, suggesting a possible link between cardiac and cerebral channelopathy. SUDEP is the most common cause of epilepsy-related mortality.

The relations between epilepsy and heart are complex and expressed in two opposite sides. (I) Cardiac arrhythmias may provoke epileptic seizures but, in this case, these seizures can be considered syncopal

attacks. These clinical features have been individualized as “cardiac epilepsy”, however, true epileptic seizures could be observed in the course of a syncopal attack and a syncope may complicate the issue of an epileptic seizure. (II) On the other hand, epileptic seizures may provoke severe cardiac arrhythmias. The neural mechanisms in cardiac arrhythmias seizures could explain only few of the sudden unexpected deaths observed in epileptic patients.

It is also possible that SUDEP can be caused by the peri-ictal cardiorespiratory crisis: central apnea, bradyarrhythmia, and neurogenic pulmonary edema. Although it has been hypothesized that seizure related ventricular tachyarrhythmias are involved in SUDEP, there are not, to date, compelling evidence. Recently, in people with epilepsy abnormalities, cardiac repolarization and peri-ictal ventricular tachycardia and fibrillation have been reported in the absence of any underlying cardiac disease, too. In consequence, derangement of cardiac repolarization could predispose sudden cardiac death in people with epilepsy and could be one possible cause for SUDEP. To prevent the risk of should be SUDEP, it might be useful include antiarrhythmic medication and implantation of cardiac combined pacemaker–defibrillator devices¹⁰.

The relationship and association between cardiac and neuronal channelopathies can be important, even if in the epileptic patients cardiac arrhythmia was not recognized/diagnosed before their sudden death. Also in presence of a causative monogenic mutation in one of the well-known channel genes (sometimes detected by non-invasive neuroimaging¹¹, it is difficult to speculate if the two phenotypes (anomalies) are arising contemporaneously (as recently speculated¹² or not.

It is important to remember that Brugada Syndrome is another example of cardiac channelopathy; it is a real dangerous situation that, in rare cases, can determine sudden cardiac death¹³.

Conclusions

The knowledge and understanding of channelopathies have helped pediatricians to elucidate some causes of epilepsy; moreover, it is possible that the activity of some ion channels can have a crucial role for the cardiac dysfunction often present in epileptic patients; modulations of the activity of these channels will offer novel therapeutic tools for these patients. Finally, also SUDEP can be related to some channel dysfunction(s) present in a certain percentage of epileptic patients.

Abbreviations

LQTS = Long QT syndrome; SUDEP = Sudden Unexpected Death in Epilepsy; TRP = Transient Receptor Potential; NMDA = N-methyl-D-aspartate.

Authors' contributions

All authors wrote, read and approved the final manuscript.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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