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Physiology

SODIUM CHANNELOPATHIES: A REVIEW

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ABSTRACT **Introduction:** Sodium channelopathies are a group of genetic disorders characterized by abnormalities in sodium channels that can cause a wide range of cardiac and neurological symptoms. These disorders can be inherited in an autosomal dominant pattern and can be caused by mutations in various genes, including SCN5A, SCN1B, and SCN2B. **Methodology:** A comprehensive literature search was conducted using PubMed, MEDLINE, and Google Scholar to identify relevant articles published from March 2005 to November 2021. The following keywords were used: "sodium channelopathies", "sodium channels", "sodium channelopathy genetics", "sodium channelopathies-pathophysiology", "sodium channelopathies- their clinical presentations and management". Only articles written in English and reporting on human studies were included. **Clinical features and management:** The clinical presentation of these disorders can vary widely, ranging from asymptomatic to sudden cardiac death, and can be influenced by factors such as age, gender, and comorbidities. Genetic testing can aid in the diagnosis and management of these disorders, and there are several treatment options available, including medications, implantable cardioverter-defibrillators, and lifestyle modifications. **Conclusion:** While significant progress has been made in our understanding of sodium channelopathies in recent years, there is still much to learn about these complex disorders. Further research is needed to fully elucidate the underlying mechanisms of these disorders, identify novel therapeutic targets, and improve clinical outcomes for affected individuals. Nonetheless, the knowledge gained so far has provided valuable insights into the pathogenesis and management of these disorders, and has the potential to greatly improve the lives of those affected by sodium channelopathies.

KEYWORDS : Sodium channelopathies, Cardiac sodium channels, Musculoskeletal, Genetic testing.

INTRODUCTION

Sodium channelopathies are a group of inherited disorders that result from mutations in genes encoding sodium channels. These channels are essential for the proper functioning of excitable cells, such as neurons and muscle cells, which rely on them for the generation and propagation of electrical impulses. Sodium channels are composed of several subunits, the alpha subunit forming the pore through which sodium ions pass. Mutations in genes encoding these subunits can lead to altered channel function, resulting in a range of clinical manifestations. The severity of these manifestations depends on the specific mutation and its effect on channel function. Some mutations lead to hyper excitability, resulting in seizures or muscle spasms, while others impair channel function, leading to muscle weakness or paralysis. There are several types of sodium channelo pathies, including epilepsy, periodic paralysis, myotonia, and cardiac arrhythmias. These disorders can be inherited in an autosomal dominant or recessive manner, and some may also occur sporadically. Diagnosis is typically made through genetic testing, along with a thorough evaluation of clinical symptoms. Research into sodium channelopathies is ongoing, with the goal of developing targeted therapies to improve outcomes for affected individuals. This includes the development of drugs that specifically target mutated sodium channels, as well as the use of gene therapy to correct genetic defects. Ultimately, a better understanding of the underlying mechanisms of sodium channelopathies will be critical for the development of effective treatments and management strategies. Here we present a systematic review of the current knowledge on sodium channelopathies, focusing on their clinical features, genetics, pathophysiology, diagnosis, and management.

METHODOLOGY

A comprehensive literature search was conducted using PubMed, MEDLINE, and Google Scholar to identify relevant articles published from March 2005 to November 2021. The following keywords were used: "sodium channelopathies", "sodium channels", "sodium channelopathy genetics", "sodium channelopathies-pathophysiology", "sodium channelopathies- their clinical presentations and management". Only articles written in English and reporting on human studies were included.

Genetics

Sodium channelopathies are mainly inherited in an autosomal dominant manner, but some forms can also be recessive or X-linked. Most sodium channelopathies are caused by mutations in genes encoding for sodium channel subunits, such as SCN5A (LQTS and BrS), SCN4A (HPP and PMC), or SCN10A (CCD). Other genes involved in sodium channelopathies include KCNE1 (LQTS), CACNA1S (HPP), and CLCN1 (PMC). The penetrance and expressivity of sodium channelopathies can vary, even within families carrying the same mutation, and can be influenced by environmental factors.(1)

Sodium channelopathies are caused by mutations in genes that encode for the various subunits of the sodium channels. The sodium channel alpha subunit genes (SCN1A, SCN2A, SCN3A, and SCN8A) are the most commonly affected genes in sodium channelopathies. SCN1A mutations, in particular, have been associated with a range of epileptic disorders, including Dravet syndrome, generalized epilepsy with febrile seizures plus (GEFS+), and severe myoclonic epilepsy of infancy (SMEI).(2). SCN2A mutations have been linked to a range of neurological conditions, including benign familial infantile seizures, early infantile epileptic encephalopathy, and autism spectrum disorder.(3) SCN4A mutations, which affect the skeletal muscle sodium channels, have been associated with a range of myotonic disorders, including hyperkalemic periodic paralysis and paramyotonia congenita.(4)

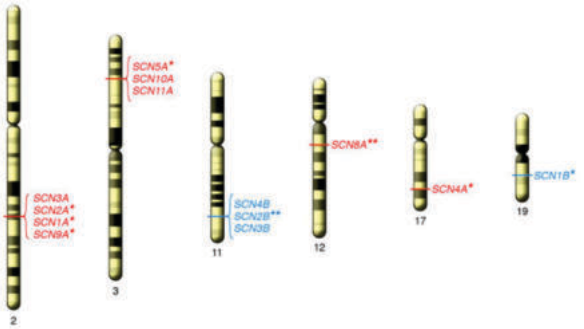

Fig: Genomic location of human Na_vChs. Chromosomal location of human genes encoding (red) and (blue) subunits across the genome. An asterisk next to the gene name indicates association with an inherited human disease. A double asterisk indicates association with murine phenotypes.(5)

Pathophysiology

The pathophysiology of sodium channelopathies is complex and not fully understood. In general, sodium channelopathies are characterized by gain-of-function or loss-of-function defects in sodium channel activity, leading to abnormal excitability or conduction properties of excitable cells.(6). For example, in LQTS, mutations in SCN5A or KCNE1 can cause delayed repolarization and increased susceptibility to early afterdepolarizations, which can trigger torsades de pointes. In BrS, mutations in SCN5A or other genes can cause reduced sodium current in the right ventricular outflow tract, leading to accentuated transmural dispersion of repolarization and creation of a vulnerable substrate for ventricular arrhythmias. (7). In HPP and PMC, mutations in SCN4A can cause increased or decreased sodium channel activity, leading to altered membrane excitability and abnormal muscle function.(8)

The pathophysiology of sodium channelopathies can vary depending on the specific type of mutation and the location of the affected channel. In general, however, these mutations can alter the normal function of the sodium channel in several ways, including changing the channel's gating properties (i.e. how it opens and closes), altering the amount of current that flows through the channel, and affecting the channel's ability to recover from inactivation.

These changes can have a profound impact on the excitability of cells, particularly neurons and muscle cells. For example, mutations that enhance sodium channel function can lead to hyperexcitability of neurons, causing symptoms such as seizures or muscle stiffness. Conversely, mutations that impair sodium channel function can lead to decreased excitability of neurons and muscle cells, resulting in weakness or paralysis.(9). One example of a sodium channelopathy that highlights the importance of proper sodium channel function in neuronal excitability is Dravet syndrome. This syndrome is caused by mutations in the SCN1A gene, which codes for the subunit of the voltage-gated sodium channel Nav1.1. Nav1.1 is highly expressed in inhibitory interneurons in the brain, and its dysfunction leads to hyperexcitability of these neurons, ultimately resulting in seizures and developmental delays.(10)

Another example of a sodium channelopathy that affects muscle function is hyperkalemic periodic paralysis (HYPP). This condition is caused by mutations in the SCN4A gene, which codes for the subunit of the sodium channel Nav1.4, which is primarily expressed in skeletal muscle cells. HYPP is characterized by episodes of muscle weakness and paralysis that are triggered by high levels of potassium in the blood. These episodes are thought to be caused by increased sodium channel activity due to altered gating properties of the mutated Nav1.4 channel.(11)

Overall, the pathophysiology of sodium channelopathies is complex and can vary widely depending on the specific mutation and affected channel. However, by studying these diseases, researchers can gain valuable insights into the normal function of sodium channels and their role in cellular excitability.

To elaborate further, sodium channelopathies are classified into gain-of-function (GoF) and loss-of-function (LoF) disorders, depending on the effect of the mutation on the sodium channel function. GoF mutations generally cause increased sodium channel activity, while LoF mutations lead to decreased channel function. GoF mutations in sodium channels can cause hyperexcitability of neurons, leading to various conditions such as epilepsy, migraine, and chronic pain syndromes.(12,13) For example, mutations in SCN1A, SCN2A, and SCN8A genes, which encode the α subunit of Nav1.1, Nav1.2, and Nav1.6, respectively, have been associated with various forms of epilepsy, including Dravet syndrome, genetic epilepsy with febrile seizures plus (GEFS+), and epilepsy of infancy with migrating focal seizures (EIMFS).(14)

GoF mutations can also affect skeletal muscle function, causing conditions such as myotonia and periodic paralysis. Myotonia is characterized by delayed relaxation of skeletal muscles, leading to muscle stiffness and difficulty in relaxing the muscle after contraction. Mutations in SCN4A, which encodes the α subunit of Nav1.4, can cause hyperexcitability of skeletal muscle fibers, leading to myotonia. On the other hand, periodic paralysis is a condition characterized by episodes of muscle weakness or paralysis that occur periodically. Mutations in SCN4A can also cause periodic paralysis, with HYPP being the most well-known form of periodic paralysis caused by sodium channelopathies.(15)

LoF mutations, on the other hand, lead to decreased sodium channel activity, affecting neuronal and cardiac function. LoF mutations in the SCN5A gene, which encodes the α subunit of Nav1.5 expressed in cardiac cells, have been associated with various arrhythmia syndromes, including long QT syndrome, Brugada syndrome, and cardiac conduction disease. In the nervous system, LoF mutations in the SCN1A gene can cause generalized epilepsy with febrile seizures plus (GEFS+), while mutations in SCN9A, which encodes Nav1.7, can cause congenital insensitivity to pain (CIP).(16)

The pathophysiology of sodium channelopathies is further complicated by the fact that mutations can affect different regions of the channel, leading to distinct changes in channel function. For example, mutations in the voltage sensor domain (VSD) of sodium channels can affect channel gating, while mutations in the pore-forming domain (PFD) can affect ion selectivity and permeation.(17)

Clinical Features

The clinical presentation of sodium channelopathies is diverse and depends on the tissue involved, the specific sodium channel affected, and the type of mutation. The most common sodium channelopathies affecting the heart are long QT syndrome (LQTS), Brugada syndrome (BrS), and cardiac conduction disease (CCD). LQTS is characterized by prolonged QT interval on electrocardiogram (ECG) and predisposition to torsades de pointes ventricular tachycardia, which can lead to syncope, seizures, or sudden death.(18) BrS is characterized by coved-type ST-segment elevation in the right precordial leads on ECG and predisposition to ventricular fibrillation or sudden death, especially during sleep or rest.(19). CCD is characterized by conduction

abnormalities on ECG and predisposition to bradycardia, heart block, or sudden death. Sodium channelopathies affecting skeletal muscle include hyperkalemic periodic paralysis (HPP) and paramyotonia congenita (PMC). HPP is characterized by episodes of muscle weakness or paralysis triggered by high potassium intake or rest after exercise, whereas PMC is characterized by muscle stiffness or myotonia aggravated by cold or exercise.(20)

Epileptic Disorders

Sodium channelopathies have been associated with a range of epileptic disorders, including Dravet syndrome, SMEI, GEFS+, and benign familial infantile seizures. Dravet syndrome, also known as severe myoclonic epilepsy of infancy, is a severe epileptic encephalopathy that typically presents in the first year of life.(12). Children with Dravet syndrome experience recurrent seizures that are often triggered by fever or other environmental stimuli.(21). Other features of Dravet syndrome include cognitive impairment, ataxia, and developmental delays.(22). SMEI, also known as Dravet syndrome variant, is a milder form of Dravet syndrome that presents later in childhood and has a better prognosis. (23) GEFS+ is a genetic epilepsy syndrome that is characterized by a range of seizure types, including febrile seizures, absence seizures, and generalized tonic-clonic seizures.(24) Benign familial infantile seizures are a relatively mild form of epilepsy that typically presents in the first few months of life and resolves by the age of two.(25)

Cardiac Arrhythmias

Sodium channelopathies can also cause a range of cardiac arrhythmias, including Brugada syndrome, long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT). Brugada syndrome is a rare inherited arrhythmia disorder that is characterized by ST segment elevation in the right precordial leads of the electro cardiogram (ECG). Patients with Brugada syndrome are at increased risk of sudden cardiac death due to ventricular fibrillation. Long QT syndrome is another inherited arrhythmia disorder that is characterized by a prolonged QT interval on the ECG. Patients with long QT syndrome are at increased risk of torsades de pointes, a potentially life-threatening arrhythmia. CPVT is a rare arrhythmia disorder that is characterized by ventricular tachycardia triggered by emotional stress or exercise.(26)

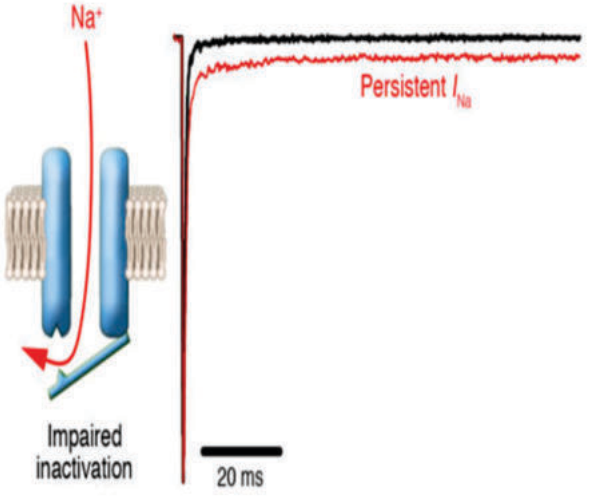

Fig : a typical instance of defective inactivation displayed by mutant NaVChs and linked to inherited epilepsy, long QT syndrome, and hyperkalemic periodic paralysis. When compared to NaVChs with normal inactivation, the defect is brought on by the inactivation gate's (left panel) incomplete closure, which results in a higher amount of persistent current (right panel, red trace) (black trace).(5)

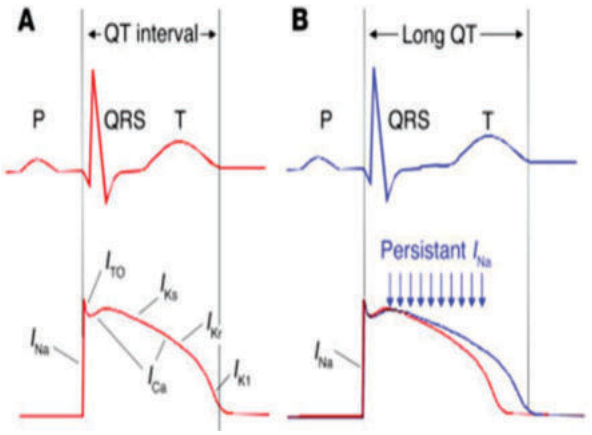

Fig : LQTS has an electrophysiological foundation. Relationship between a typical cardiac action potential and the surface ECG (top) in figure (A) (bottom). The action potential length is roughly represented by the QT interval. There are labels for the specific ionic currents that cause the action potential's various stages. (B)

A persistent sodium current causes the QT gap to lengthen and an abnormal cardiac action potential (blue) to follow. INa, sodium current; ICa, calcium current; ITO, transient outward current; IKr, rapid component of delayed rectifier current; IKs, sluggish component of delayed rectifier current.(5)

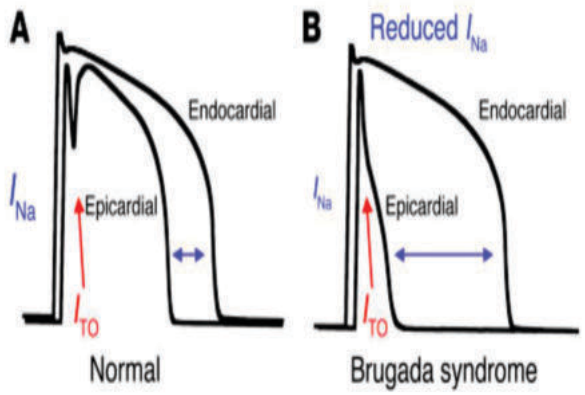

Fig : Brugada syndrome's electrophysiological foundation. The typical heart's endocardial and epicardial action potentials are contrasted in Figure 1(A).

Because of a significant transitory outward current, the epicardial action potential is shorter. (B) Brugada syndrome endocardial and epicardial action potentials. Epicardial action potentials are disproportionately shortened by reduced sodium current, which magnifies the transmural voltage gradient (horizontal double arrow).(5)

Myotonic Disorders

Sodium channelopathies can also affect the skeletal muscles, leading to myotonic disorders such as hyperkalemic periodic paralysis, paramyotonia congenita, and potassium-aggravated myotonia. Hyperkalemic periodic paralysis is a rare genetic disorder that is characterized by episodic muscle weakness that is typically triggered by high levels of potassium in the blood.(27).

Paramyotonia congenita is another rare genetic disorder that is characterized by muscle stiffness and weakness that is worsened by cold temperatures and exercise. Potassium-aggravated myotonia is a milder form of myotonia that is characterized by muscle stiffness and weakness that is triggered by high levels of potassium in the blood.(28)

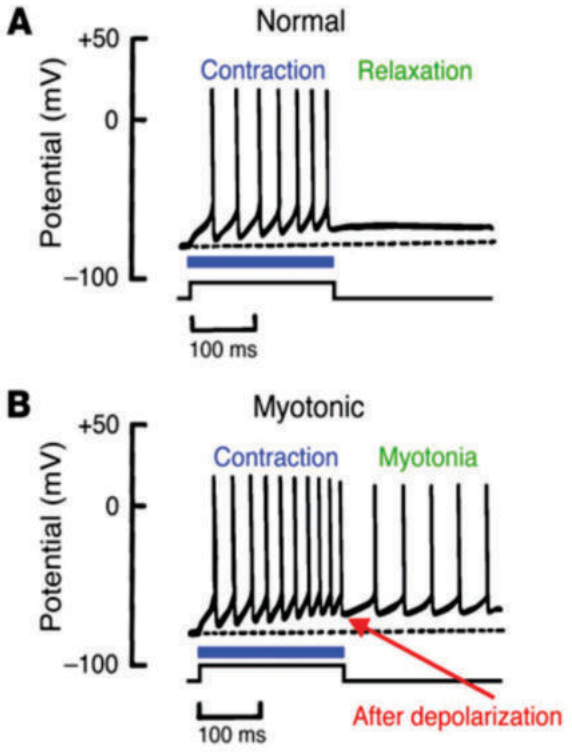

Fig : Differences between normal and myotonic muscle action potentials. (**A**) Generation of action potential spikes during electrical stimulation (horizontal blue line and square wave) of a normal muscle fiber. Contraction occurs during action potential firing, followed by muscle relaxation when stimulation ceases. (**B**) Action potentials in myotonic muscle during and immediately after electrical stimulation. An afterdepolarization triggers spontaneous action potentials that fire after termination of the electrical stimulus (myotonic activity).(5)

Diagnosis

The diagnosis of sodium channelopathies requires a comprehensive evaluation of clinical, genetic, and electro physiological features. Clinical evaluation includes a detailed family history, physical examination, and ECG monitoring. Genetic testing can confirm the presence of a known mutation or identify a new mutation in the affected individual or their family members. Electrophysiological testing, such as provocative testing, can assess the inducibility of arrhythmias or muscle weakness in sodium channelopathies. Provocative testing involves administering specific drugs or maneuvers that can trigger arrhythmias or muscle weakness in susceptible individuals.(1,15,18)

Management

The management of sodium channelopathies depends on the specific clinical phenotype and the risk of adverse events. In general, treatment aims to reduce the risk of arrhythmias, syncope, or sudden death, and to alleviate symptoms such as muscle weakness or stiffness. Treatment options include lifestyle modifications, medications, and invasive procedures such as implantable cardioverter-defibrillator (ICD) placement or muscle biopsy. Lifestyle modifications such as avoidance of triggers, regular exercise, and adequate hydration can reduce the frequency of arrhythmias or muscle weakness in sodium channelopathies. Medications such as beta-blockers, sodium channel blockers, or potassium channel openers can also be used to prevent arrhythmias or alleviate symptoms in sodium channelopathies. ICD placement is recommended in high-risk individuals with LQTS or BrS, whereas muscle biopsy can confirm the diagnosis and guide the management of HPP or PMC.(29,30)

Prevention and early intervention

It is important to note that while sodium channelopathies are relatively rare, they can have serious and potentially life-threatening consequences. Therefore, early detection and appropriate management of these disorders is essential. Clinicians should maintain a high index of suspicion for sodium channelopathies in patients with unexplained cardiac or neurological symptoms, especially in those with a family history of sudden cardiac death or inherited arrhythmia syndromes.(1)

Additionally, genetic counseling is an important aspect of the management of sodium channelopathies, as it can help affected individuals and their families understand the inheritance patterns of these disorders, the risks of passing them on to future generations, and the options available for genetic testing and family planning.(31)

CONCLUSION

Sodium channelopathies are a group of genetic disorders affecting sodium channels in excitable cells, leading to a range of clinical phenotypes such as arrhythmias, conduction abnormalities, or muscle weakness. The diagnosis of sodium channelopathies requires a comprehensive evaluation of clinical, genetic, and electro physiological features. Treatment aims to reduce the risk of adverse events and alleviate symptoms, and includes lifestyle modifications, medications, and invasive procedures such as ICD placement or muscle biopsy. Future research should focus on improving the understanding of the pathophysiology of sodium channelopathies and developing more effective and personalized treatments.

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