ISSN 1022-7954, Russian Journal of Genetics, 2018, Vol. 54, No. 1, pp. 45–56. © Pleiades Publishing, Inc., 2018.
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REVIEWS
AND THEORETICAL ARTICLES

Sodium Channelopathies: From Molecular Physiology towards Medical Genetics

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Received January 30, 2017; in final form, February 22, 2017

Abstract—Voltage-gated sodium channels are heteromeric transmembrane proteins involved in the conduction of sodium ion currents in response to membrane depolarization. In humans, nine homologous genes, *SCN1A–11A*, which encode different isoforms of the voltage-gated sodium channel family, are known. Sodium channel isoforms exhibit different kinetic properties that determine different types of neurons. Mutations in different channels are described in patients with various congenital disorders, from epilepsy to congenital insensitivity to pain. This review presents an analysis of the current literature on the properties of different isoforms of voltage-gated sodium channels and associated diseases.

Keywords: voltage-gated sodium channels, structure, expression, medical genetics, hereditary diseases, mutations

DOI: 10.1134/S102279541801009X

INTRODUCTION

In animal cells, electrical signals are used to transmit and distribute information often over fairly long distances [1]. Various protein complexes called ion channels form hydrophilic pathways inside the plasma membrane and catalyze the ion flow through the lipid bilayer, which otherwise would be virtually impossible owing to the high potential barrier generated by the plasma membrane. Thus, ion channels provide selective permeability of the membrane owing to the facilitated diffusion of ions, which plays a key role in the interaction of cells. The emergence of nerve cells during the evolution of animals emphasized rapid electrical interactions provided by voltage-gated sodium channels (Na_V), which determine the selective flux of sodium ions through the plasma membrane and can quickly open and close in response to changes in the membrane potential. This, in turn, regulates the permeability of the membrane for sodium ions and leads to the generation of an action potential [2, 3].

Voltage-gated sodium channels are responsible for the generation of an action potential and its distribution in excitable cells: muscle, nervous, and neuroendocrine cells. They are also expressed at a low level in nonexcitable cells, where their function is still unclear [4].

Sodium channels consist of highly processed α-subunits of about 260 kDa, associated with additional β-subunits [5]. Expression of α-subunits that form the pore for sodium ions is sufficient for the manifestation of the conductive function; however, the kinetics and dependence of the channel function on the potential are modified by accessory β-subunits, which determine subcellular localization of the channel and interaction with adhesion proteins, extracellular matrix, and cytoskeleton. α-Subunits are organized as four homologous domains (DI–DIV); each of them consists of six transmembrane α-helices (S1–S6) and an additional loop between the S5 and S6 segments, which forms the pore (Fig. 1). The pore loops form a wider channel entrance for the ions, while the S5 and S6 helices form a narrower exit from the channel for the ions, which is directed into the interior of the cell. The S4 segment of each domain contains positively charged amino acid residues in every third position, which serve as sensors for a change in the resting membrane potential capable of altering the conformation and leading to the channel activation in response to membrane depolarization. A short intracellular loop that connects the transmembrane domains III and IV serves as a channel-inactivating sensor, which leads to the closure of the channel pore from inside during a prolonged depolarization of the membrane [4].

MOLECULAR STRUCTURE

Initial attempts to establish the structure of voltage-gated sodium channels were made more than 30 years ago in the study of covalently labeled channel

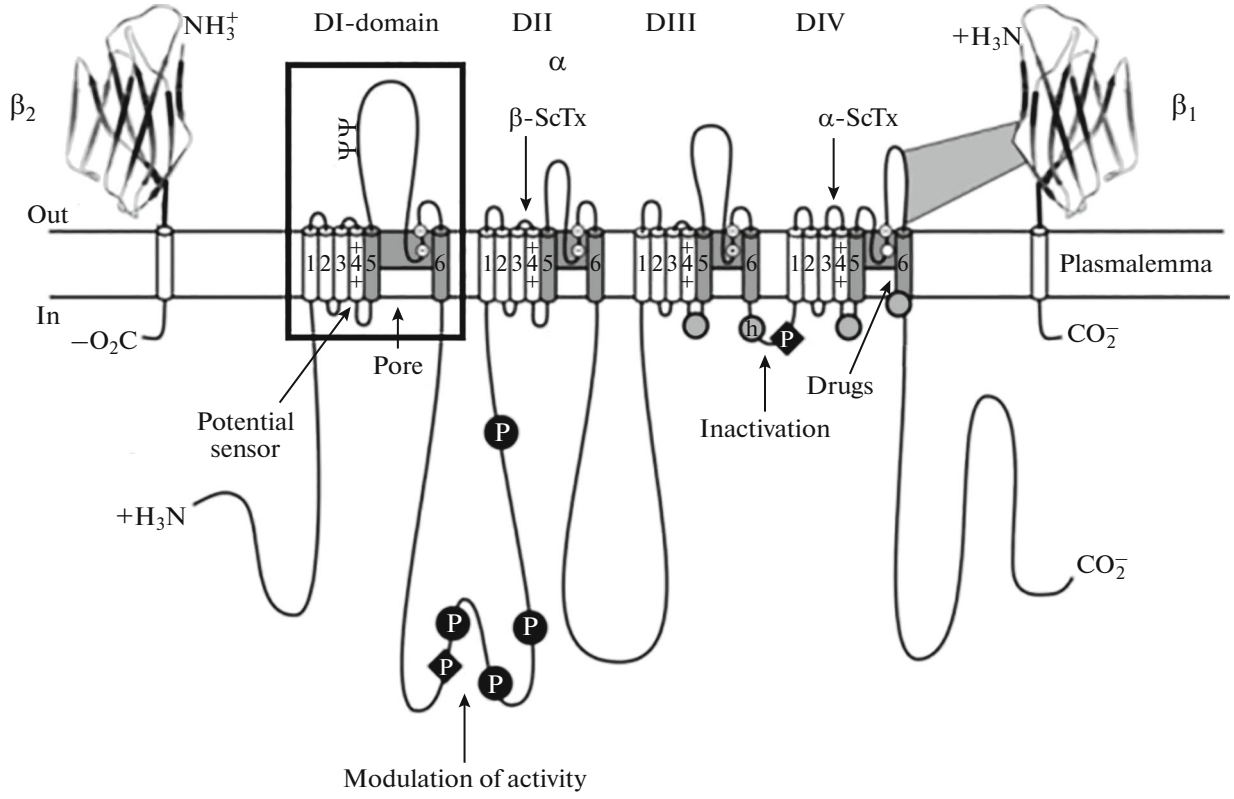

Fig. 1. Organization of voltage-gated sodium channels within the plasma membrane. Structure is shown by an array of transmembrane domains. Cylinders denote transmembrane α-helices. Fatty line illustrates the amino acid chain of each subunit with lengths approximately proportional to the number of amino acid residues in each of the subunits. Extracellular domains of β1 and β2 subunits are represented as immunoglobulin-like structures. Ψ are probable N-glycosylation sites; P are phosphorylation sites of protein kinase A (delineated with circles) or protein kinase C (delineated with rhombuses). Shaded cylinders represent S5–P–S6 segments overlaying the surface of ion-conducting pore. White small circles show external (EEDD) and internal (DEKA) rings of amino acid residues forming ion-selective filter and tetrodotoxin (TTX) binding sites. Sign "++" designates transmembrane potential sensors formed by S4 segments. Symbol "h" in the filled circle indicates inactivating loop of the channel, containing four amino acid residues (IFMT), which binds to channel inactivating receptor, which is formed by regions of intracellular loops, indicated by empty colored circles. In addition, scheme shows binding sites with α- and β-toxins of scorpion venom, as well as the site of α- and β1-subunit interaction.

components using a photoactive toxin from scorpion venom [6–8]. Significant progress in this direction was achieved after the determination of the primary structure of the human genome was completed, and 143 genes encoding proteins of various ion channels were identified. X-ray crystallography of prokaryotic sodium channels played an important role, because it made it possible to visualize the three-dimensional structure of sodium channels in various functional states [9–12]. When combining the data on the primary structure of human channels with the crystallographic data of bacterial proteins, it became possible to simulate eukaryotic sodium channels on the basis of their structural homology by molecular dynamics methods [13, 14]. Nevertheless, the decoding of the tertiary structure of eukaryotic channels is an open question, the answer to which will allow a deeper understanding of their functioning at the molecular level.

Molecular Architecture of α-Subunits

Eukaryotic voltage-gated sodium channels consist of an α-subunit that can be linked to one or two β-subunits. Nine α-subunits $Na_V1.1$, $Na_V1.2$, $Na_V1.3$, $Na_V1.4$, $Na_V1.5$, $Na_V1.6$, $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$, encoded by the genes *SCN1A*, *SCN2A*, *SCN3A*, *SCN4A*, *SCN5A*, *SCN8A*, *SCN9A*, *SCN10A*, and *SCN11A*, respectively, are found in humans. Different α-subunits determine different subtypes of sodium channels and contain binding sites for various drugs and toxins. α-Subunits are large polypeptides of about 2000 amino acid residues, which constitute four homologous domains denoted as DI–DIV, which form a pseudotetrameric structure (Fig. 1). The structural homology of various voltage-gated sodium channels is very high in mammals, and it is more than 50% in transmembrane and extracellular regions [4]. Each domain consists of six transmembrane helical segments, called S1–S6. Prokaryotic sodium channels are much simpler and are formed by homotetramers of

identical polypeptide chains consisting of six transmembrane segments (S1–S6) and showing a high degree of homology with each of the domains of a single eukaryotic α-subunit.

Voltage-sensing domain (VSD). The S1–S4 segments of the α-subunit form the sensory domain necessary for the regulation of the channel opening in response to membrane depolarization. The voltage-sensing domain has a certain mobility, mediated by the presence of positively charged arginine and lysine residues located in each third position of the segment S4 chain. Four voltage-sensing domains are organized in the membrane around the central hydrophilic channel, which forms the pore of the channel. The voltage sensor is associated with the pore-forming domain through the intracellular loop between the S4 and S5 helices. When the membrane is depolarized, the positively charged transmembrane helix S4 shifts toward the outer surface of the membrane. This movement is transferred to the pore domain through intracellular linkers, which leads to conformational changes in the pore and its opening. Further drop in the potentials difference across the membrane results in inactivation of the channel by changing the position of the inactivation gates (formed by the interdomain linker DIII–DIV) into the pore cavity. Subsequent repolarization causes the S4 helix to return to its resting state and the channel becomes ready for the next activation cycle [15].

Pore domain (PD). The S5 and S6 segments and the extracellular loop linking them (P loop) form the channel pore and selectivity filter. Most blocking drugs inactivating sodium channels bind specifically to the amino acid residues of the central hydrophilic surface of the channel pore. Recent structural studies of voltage-gated sodium channels showed the presence of additional holes in the extracellular surface of the channel, which provide additional lateral access of various ions and small molecule compounds to the pore [16, 17].

Selectivity filter (SF). The selectivity filter is the narrowest part of the pore and is necessary for selectively passing different ions of similar charge and radius. A single polypeptide chain of eukaryotic voltage-gated sodium channels provides an asymmetric distribution of the amino acid residues forming the selectivity filter: aspartate (D) in the DI domain, glutamate (E) in DII, lysine (K) in DIII, and alanine (A) in DIV (the so-called DEKA motif). Geometrically, these amino acid residues form the narrowest region of the ion channel pore, which is called the inner ring and ensures the passing of only hydrated sodium ions through the pore. The ionic bond between the lysine residue and glutamate or aspartate is required for the regulation of the size of the pore that can hold Na^+ ions much more efficiently than K^+ ions, although the spatial distribution of the free energy of these cations plays a certain role in the channel specificity. The complete loss of selectivity for Na^+ ions occurs when the lysine residue at position 1237 is replaced with glutamate, which makes the channel permeable to Na^+, K^+, Ca^{2+}, and Ba^{2+} ions [18]. More superficially, on the side of the extracellular space, there is the so-called outer ring of the selectivity filter formed by two glutamates and two aspartates (EEDD), which play a certain role in the permeability for sodium cations. Currently, the following ion selectivity model is proposed. Lysine residues are apparently necessary for electrostatic progression of Na^+ cations from the outer ring of the selectivity filter to the cluster of carboxyl groups formed by the residues of glutamate and aspartate [19]. In addition, it was shown that Na^+ progresses along the pore eccentrically at a distance of 5 Å from the geometric central axis of the pore owing to the uneven distribution of the amino acid residues that form the pore in the pseudotetrameric α-subunit [20].

Inactivation gate. Another key structural element of the α-subunit of voltage-gated sodium channels is the inactivation gate (Fig. 1) formed by the intracellular loop linking the DIII and DIV domains. The inactivation gate blocks the ion flow, sheltering the ionic pore from the cytoplasm during rapid channel inactivation [5].

Activation gate. Four hydrophobic amino acid residues located one on the cytoplasmic side of each of the S6 segments form a small intracellular cavity called activation gate (Fig. 1). For example, the activation gate is formed by four aromatic residues in the wild type $Na_V1.7$ channel (Y405 in the S6 segment of the DI domain, F960 in the DII domain, F1449 in DIII, and F1752 in DIV). It was shown that, under the deletion of the L955 residue in the DIVS6 segment, the F960 orientation is changed more radially toward the DIIIS6 segment, which leads to a disruption in the structure of the activation gate [21]. This causes a hyperpolarization shift in the voltage dependence of the channel activation [22]. As a consequence, the mutant $Na_V1.7$ channel is activated under a more polarized state of the membrane, which leads to hyperexcitability of $Na_V1.7$ expressing neurons of dorsal root ganglion (DRG), causing a sense of pain in carriers of such a deletion. Nevertheless, the precise position of the activation gate of the voltage-gated sodium channels remains unknown. Comparative genomic data serve as an additional indication of the functional importance of four hydrophobic amino acid residues at the intracellular end of each S6 segment [23].

Sensitivity of sodium channels to protons. It is known that a change in the extracellular concentration of hydrogen ions leads to a change in the inactivation characteristics of voltage-gated sodium channels [24]. When studying the electrophysiological properties of the $Na_V1.5$ channel expressed in the cardiac muscle, it was shown that amino acid residues C373 and H880 localized in the P loop act as a proton sensor. Protonation of these residues due to the decrease in extracel-

lular pH affects the function of $Na_V1.5$ and may lead to cardiac arrhythmia [25].

Molecular Architecture of β-Subunits

As mentioned above, eukaryotic voltage-gated sodium channels consist of one α-subunit, which may be linked to one or two β-subunits. In mammals, four genes (*SCN1B–SCN4B*) encoding five different β-subunits, designated as β1, β1B, β2, β3, and β4, are found in the genome. The β2 and β4 subunits bind to the α-subunit by a disulfide bond, while β1 and β3 bind noncovalently. The β-subunits are transmembrane proteins with the exception of β1B, which is a soluble molecule. Although one α-subunit is sufficient to form a functional voltage-gated sodium channel, β-subunits are required for proper functioning and expression of the channel on the cell surface. The β-subunits of voltage-gated sodium channels are members of the immunoglobulin (Ig) superfamily of cell adhesion molecules (CAMs) that expose the Ig domain to the extracellular medium [26]. More detailed studies of the β3 subunit showed that it can trimerize with its Ig domains. In addition, it was shown that the α-subunit of the $Na_V1.5$ channel binds to the β3 subunit by four different sites, which may indicate the possibility of α-subunit oligomerization of the channels in vivo [27]. Functionally, β-subunits participate in the inactivation of the opened channel, as shown by the example of the β4 subunit in the human embryonic kidney cell line HEK293T [28].

GENERAL PHYSIOLOGY

Voltage-gated sodium channels are expressed on the cell membranes of excitable and nonexcitable cells. The activation of sodium channels depends on the membrane potential, which determines the state of the membrane potential sensor. Hyperpolarization of the membrane makes the activation of the channel under the state of rest very unlikely. Depolarization of the membrane leads to conformational changes of the α-subunit caused by the movement of the potential sensor inside the membrane. These changes lead to the opening of the sodium-selective ion pore. Voltage-gated sodium channels open very quickly and mediate the flow of sodium ions directed into the cell, which causes rapid generation of the action potential in excitable cells. Milliseconds later, the channel transfers into an inactive state. A decrease in sodium currents which occurs in response to a short depolarization owing to the closing of the intracellular inactivation gate is called rapid inactivation. Slow inactivation occurs in nerve and muscle cells under the influence of a long (within seconds) depolarization, which leads to a prolonged change in the resting potential on the membrane, or during prolonged repeated generations of the action potential [13]. In general, voltage-gated sodium channels are kinetically fast channels that become closed (inactivated) within a few milliseconds. However, some subtypes of sodium channels undergo incomplete rapid inactivation, which can lead to persistent sodium currents, which was shown in the case of $Na_V1.9$ in sensory neurons or under certain conditions for $Na_V1.4$ and $Na_V1.6$ subtypes in muscle cells and Purkinje neurons, respectively [29, 30]. Mutations in the genes *SCN1A*, *SCN2A*, *SCN3A*, and *SCN8A*, resulting in defects in the inactivation gate functioning, cause an increase in persistent currents and lead to various forms of ataxia and epilepsy [31].

In some types of neurons, voltage-gated sodium channels open again after rapid inactivation during membrane repolarization. This temporary opening of the channels is called resurgent current and causes a massive current of sodium ions directed into the cell. It is believed that the emergence of the resurgent currents is determined by the elimination of the inactivating influence of β-subunits. The resurgent currents are associated with chronic painful conditions caused by their intensification under the influence of various inflammatory mediators (bradykinin, histamine, prostaglandin E2, ATP) owing to mutations of the $Na_V1.7$ channel in the dorsal root ganglion neurons [32–34]. Changes in the domains of sodium channels underlie the pathogenesis of diseases associated with them, as will be discussed below. In addition, sodium channels are expressed in cells that are not considered excitable, for example, astrocytes, microglia, macrophages, and certain types of tumor cells, where they participate in phagocytosis, regulation of cell mobility, and metastasis. These interesting features of sodium channels are detailed in the reviews [35, 36].

EXPRESSION

In addition to differences in cellular and tissue expression in mammals, sodium channels also have differential expression profiles during development of the organism and various subcellular localizations that depend on the specific role of each channel in mammalian physiology. In rodents, $Na_V1.3$ is expressed in embryonic nerve tissues, while $Na_V1.1$, $Na_V1.2$, and $Na_V1.6$ are strongly represented in the central nervous system of the adult organism. As a rule, $Na_V1.1$ and $Na_V1.3$ are localized on the soma, where they can regulate the process of integrating signals of synaptic impulses to establish the threshold for generating the action potential and its distribution in dendritic and axonal compartments. Data of immunohistochemical experiments indicate that $Na_V1.2$ is expressed in unmyelinated axons, where it participates in the generation of the action potential [37]. As it was shown, during the development process, $Na_V1.6$ replaces the $Na_V1.2$ channel in the maturation period of the nodes of Ranvier, through which the saltatory conduction of the action potential is performed [38, 39].

$Na_V1.1$ and $Na_V1.6$ are also strongly represented in the peripheral nervous system (PNS). But the channels $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$, which were cloned from sympathetic and spinal ganglion neurons, are the most abundantly expressed. Among them, $Na_V1.7$ is widely expressed in PNS and appears to be localized in axons, where it can function in the generation and conduction of the action potential [40]. Narrower expression patterns are observed for the $Na_V1.8$ and $Na_V1.9$ channels; these channels are differentially expressed in small sensory neurons of the dorsal root and ganglion of the trigeminal nerve, where they play a key role in the perception of pain [41, 42]. Finally, $Na_V1.4$ and $Na_V1.5$ are muscular sodium channels that control the excitability of skeletal and cardiac myocytes, respectively. $Na_V1.5$ is expressed at the middle level during the development of skeletal muscles, but is replaced by the $Na_V1.4$ channel in adults [43].

The functioning of sodium channels is the most interesting in neurons of the brain. In order to understand the effect of sodium channels on synaptic signal transmission, it is important to know what isoforms of sodium channels are present in each type of neurons, as well as their properties and distributions. In the mammalian cerebellum, four different α-subunits are represented: $Na_V1.1$, $Na_V1.2$, $Na_V1.3$, and $Na_V1.6$. Three isoforms of β-subunits (Naβ1–3) are present in the cerebellum; however, the expression of $Na_V1.3$ and Naβ3 is detected only during the development. Using in situ hybridization and immunolocalization methods, it was shown that $Na_V1.2$, $Na_V1.6$, Naβ1, and Naβ2 are predominantly expressed in granular cells. Channels $Na_V1.2$ and $Na_V1.6$ are mainly localized in parallel fibers of granular cells. Purkinje cells express $Na_V1.1$, $Na_V1.6$, Naβ1, and Naβ2. Neurons of the deep cerebellar nuclei express $Na_V1.1$ and $Na_V1.6$, as well as Naβ1. Bergmann glia express $Na_V1.6$.

HEREDITARY CHANNELOPATHIES

Mutations in the genes of voltage-gated sodium channels may result in the emergence of a wide range of hereditary diseases affecting skeletal muscles, the cardiovascular system, and the nervous system. Clinical severity of these diseases ranges from moderate or even latent to life-threatening conditions that lead to disability. Sodium channelopathies were one of the first investigated diseases caused by the impairment of the ion channel functioning, and they continue to attract a wide clinical and scientific interest to this day.

Most of the sodium channelopathies are dominantly heritable, but some of them are recessive or appear sporadically. In addition, several pharmacogenetic syndromes are also associated with variants in the genes of voltage-gated sodium channels. The clinical manifestations of these diseases depend, first of all, on the expression pattern of the mutant gene at the tissue level and the biophysical nature of the sodium channel dysfunction at the molecular level. It is also worth noting that the expression of many sodium channels is increased in various types of cancer [44].

Channelopathies can be divided into four groups of diseases depending on the organ mainly involved in pathogenesis (Table 1):

(1) *Sodium channelopathies of the brain*, which are associated with mutations in *SCN1A*, *SCN2A*, *SCN1B*, and some mutations in *SCN8A* observed in cases of familial ataxia and early epilepsy (these genes encode $Na_V1.1$, $Na_V1.2$, β1-subunit, and $Na_V1.6$, respectively).

(2) *Sodium channelopathies of skeletal muscles.* This group includes mutations in the *SCN4A* gene encoding the $Na_V1.4$ isoform, which is specifically expressed in skeletal muscles. Mutations in SCN4A are associated with myotonia, myasthenic syndrome, and periodic paralysis.

(3) *Sodium channelopathies of the heart* associated with mutations in *SCN5A* (the gene that encodes $Na_V1.5$ is predominantly expressed in the cardiac muscle) and *SCN10A* (the gene encoding $Na_V1.8$ was found during genome-wide association studies (GWAS) with changes in ventricular conduction [45]).

(4) *Sodium channelopathies of peripheral nerves* include mutations in *SCN9A* ($Na_V1.7$), *SCN10A* ($Na_V1.8$), and *SCN11A* ($Na_V1.9$). The mutations in these genes are associated with peripheral pain syndromes, including those with neuropathic and inflammatory pain.

Sodium Channelopathies of the Brain

Mutations in the *SCN1A* gene are most often found in sodium channelopathies of the brain. Data obtained in the murine model of Dravet syndrome in which truncated $Na_V1.1$ is expressed showed that the loss of the function of this channel causes a decrease in the sodium current and excitability in GABAergic neurons [46]. Missense mutations in $Na_V1.1$ may cause the loss of the function because of a disturbance of the channel folding. The phenotype of such mutants in the cell culture can be restored through molecular interactions with coexpressing proteins and drugs. Epilepsy also occurs owing to mutations in *SCN1A*, which alter the character of the channel inactivation, resulting in a constant current of sodium ions directed inside the cell (the effect of enhancing the function owing to a mutation leading to hyperexcitability) [47]. In general, one can say that functional studies of $Na_V1.1$ mutant variants revealed a wide range of biophysical phenotypes from the loss of the function to its amplification. At first glance, it seems that these effects contradict each other from the etiopathogenetic point of view. Therefore, a question may arise as to how different mutations with such different func-

Table 1. Characteristics of voltage-gated sodium channels

Gene	Chromosome	Channel	Expression	Human channelopathies
SCN1A	2q24.3	$Na_V1.1$	Somata of central neurons, T-tubules of muscle fibers	Epilepsies and epileptic disorders, including febrile epilepsies and generalized epilepsies with febrile seizures (GEFS+), Dravet syndrome (severe myoclonic epilepsy of infancy), Doose syndrome (myoclonic astatic epilepsy), intractable childhood epilepsy with generalized tonic-clonic seizures, West syndrome (infantile spasms), Rasmussen's encephalitis, Lennox–Gastaut syndrome. Nonepileptic diseases: familial hemiplegic migraine, familial autism, Panayiotopoulos syndrome
SCN2A	2q24.3	$Na_V1.2$	Central neurons, mainly localized in unmyelinated and premyelinated axons	Early infantile epileptic encephalopathy, benign familial infantile seizures
SCN3A	2q24.3	$Na_V1.3$	Somata of central neurons (mainly expressed in embryonic and early prenatal period), cardiomyocytes	Potential contribution to the development of peripheral neuropathic pain after spinal cord injury
SCN4A	17q23.3	$Na_V1.4$	Skeletal muscles (high level in adult muscles, low level in neonatal muscles)	Sodium channelopathies of muscles (hyperkalemic periodic paralysis, congenital paramyotonia, potassium-aggravated myotonia, severe congenital myotonia, myasthenic syndrome, hyper-, hypo-, and normokalemic periodic paralysis, malignant hyperthermia susceptibility)
SCN5A	3p21-24	$Na_V1.5$	Cardiomyocytes, immature and denervated skeletal muscles	Cardiac sodium channelopathies: congenital long QT syndrome (Romano–Ward syndrome), idiopathic ventricular fibrillation (Brugada syndrome), isolated cardiac conduction disease, atrial asystole, sick sinus syndrome, sudden infant death syndrome, dilated cardiomyopathy, conduction disturbance, arrhythmia
SCN8A	12q13	$Na_V1.6$	Output neurons from the cerebellum, cerebral cortex, hippocampus; Purkinje cells from the layer of granular cells of the cerebellum; astrocytes and Schwann cells; dorsal root ganglia; nodes of Ranvier; T-tubules of cardiomyocytes	Early infantile epileptic encephalopathy, cerebellar ataxia in mice, end plate disease of neuromuscular junction in mice
SCN9A	2q24	$Na_V1.7$	All types of dorsal root ganglion neurons, sympathetic neurons, Schwann cells, neuroendocrine cells	Congenital insensitivity to pain, familial primary erythromelalgia, paroxysmal pain phenomenon, GEFS+
SCN10A	3p22.2	$Na_V1.8$	Dorsal root ganglion neurons, human heart, intracardiac neurons	Peripheral pain syndromes, changes in PR interval and ventricular conduction of the heart
SCN11A	3p22.2	$Na_V1.9$	C-type of dorsal root ganglion neurons	Potential role in nociception and syndromes of increased pain sensitivity
SCN7A	2q21-q23	Na_x	Dorsal root ganglion neurons, neurons of the hippocampus, thalamus, cerebellum, median preoptic nucleus, peripheral nervous system, skeletal muscle, uterus	The absence of channel in neurons can affect the ability to control fluid and ion balance of the body

tional effects can be associated with the same phenotypic manifestation in the form of epileptic states. Such heterogeneity may be due to the fact that *SCN1A* is widely expressed in most neurons of the brain. At the same time, the same mutation in *SCN1A* can lead to both hyper- and hypoexcitability, depending on the type of neurons [48]. Thus, the actual effect of *SCN1A* mutations on the electrical activity of the brain will depend not only on the type of neurons where the mutant channel is expressed but also on the electrical balance between all ion currents that contribute to this activity.

Dravet syndrome (severe myoclonic epilepsy of infancy) is a rare disease characterized by generalized tonic, clonic, or tonic-clonic seizures that are initially provoked by increasing temperature and manifested during the first year of life. Patients with Dravet syndrome usually have *de novo* mutations. Later, patients also exhibit other types of seizures, including short-term loss of consciousness and myoclonic or other types of seizures. The psychomotor delay is observed approximately in the second year of life. Dravet syndrome is considered to be the most severe phenotype within the spectrum of generalized epilepsies with febrile seizures. More than half of the mutations cause the loss of function as a result of the occurrence of premature stop codons or deletions, which leads to a decrease in the level of functional sodium channels. Mutations in *SCN1A* are also associated with other epileptic disorders, which are listed in Table 1.

Missense mutations in *SCN2A* were found in a small percentage of cases in patients with epilepsy, mainly in benign familial infantile epilepsy (BFIE). According to the data, mutations led to a decrease in the channel activity (the loss of function) [49]; other authors reported that mutations in *SCN2A* led to the effect of the gain of function [50, 51].

The first mutation in *SCN3A* (K353Q) was identified in patients with focal epilepsy resistant to antiepileptic drugs [52]. Despite the fact that the revealed missense mutation caused an increase in the late current, the pathogenic role of mutant $Na_V1.3$ is still questionable.

Sodium Channelopathies of the Skeletal Muscles

Disturbance of the function of sodium channels in muscles may affect their ability to contract or relax and is associated with two pathological conditions: myotonia and periodic paralysis [53]. Myotonia is characterized by slowed muscle relaxation after sudden forced contraction and is associated with a repetitive generation of the action potential leading to hyperexcitability of the sarcolemma. In contrast, periodic paralysis is a state of reduced excitability of the muscle cell membrane, in which the action potentials cannot be generated or distributed.

Periodic paralysis and myotonia. Periodic paralysis is characterized by episodic weakness or paralysis of contracting muscles that occurs under normal neuromuscular transmission and motor neuron function. In patients with familial periodic paralysis, the disease usually manifests itself in childhood [54]. Weakness attacks are often associated with changes in the concentration of potassium ions (K^+) in the serum as a result of a sharp redistribution of intra- and extracellular K^+. This clinical epiphenomenon forms the basis for the classification of periodic paralysis, in the form of hypo-, hyper-, or normokalemic. In congenital paramyotonia, cold-induced rigidity and weakness of the muscles are the leading symptoms [54, 55]. Potassium-aggravated myotonia is characterized by myotonia without weakness and worsening of the symptoms after intake of components with an increased content of K^+ ions [56].

Electrophysiological studies in vitro established that both myotonia and periodic paralysis are associated with abnormal conduction of sodium ions in the muscle cell membrane [57], and these results indicated the *SCN4A* gene as the most probable candidate responsible for the development of these conditions. Studies on genetic linkage confirmed this hypothesis [58]. Hyperkalemic periodic paralysis, congenital paramyotonia, and potassium-aggravated myotonia were found to be related to missense mutations in the *SCN4A* gene. Two prevailing mutations associated with hyperkalemic periodic paralysis have been described (p.T704M and p.M1592V), and they arise independently of each other in unrelated pedigrees [59, 60]. For congenital paramyotonia and potassium-aggravated myotonia, the spectrum of mutations turned out to be wider [61, 62]. In addition, about 15% of patients with hyperkalemic periodic paralysis have mutations in the *SCN4A* gene [63]. Homozygous *SCN4A* mutations are also described in congenital myasthenia [64, 65].

Characterization of SCN4A gene mutations and pathophysiology. Using heterologously expressed recombinant voltage-gated sodium channels, several laboratories characterized biophysical consequences of many mutations associated with either periodic paralysis or various myotonic disorders. These studies showed that variable defects in the rate or degree of channel inactivation occur in almost all cases. Mutations associated with hyperkalemic periodic paralysis show incomplete inactivation, which leads to a minimum level of the residual Na^+ current (1–2% of the peak current) and to a stable depolarization of muscle fibers [66, 67], which in turn results in the inactivation of the majority of sodium channels (both mutant and wild type). This explains conduction disturbance and electrical hyperexcitability observed in skeletal muscles during an attack of periodic paralysis [68, 69]. Thus, mutant sodium channels exert an indirect dominant-negative effect on normal channels. In addition,

some, but not all, mutations associated with hyperkalemic periodic paralysis have an impaired slow inactivation [70], which contributes to maintaining the effect of residual sodium current [71].

SCN4A mutations in myotonic disorders lead to a slowdown of the inactivation rate and the rate of recovery from inactivation, as well as to retardation of deactivation [72, 73]. It is assumed that these biophysical disturbances increase the duration of the action potentials in muscle fibers [74]. Elongation of the action potentials along the T tubules of myofiber membranes leads to a local increase in the extracellular potassium concentration owing to its outflow from the cell through constantly activated potassium channels. The extracellular concentration of K^+ ions in the T tubules has a depolarizing effect on the membrane. This can cause the appearance of spontaneous action potentials on the membranes of neighboring fibers, which in turn cause persistent muscle contraction and delayed relaxation, which is a symptom of myotonia [75].

Strategies for treatment of skeletal muscle sodium channelopathies. At present, carbonic anhydrase inhibitors are used for pharmacological treatment of sodium channelopathies of muscles, but the mechanism of their action has been little studied [76, 77]. Some local anesthetic/antiarrhythmic drugs have antimyotonic activity and are sometimes suitable for the treatment of nondystrophic myotonias [78, 79]. These drugs are effective owing to their ability to interrupt fast-acting series of the action potentials through their blocking activity toward sodium channels. Mexiletine is the most commonly used antimyotonic agent, whose effectiveness was demonstrated in experiments in vitro [80], but no clinical trials that compare this agent with a placebo or with other treatments have been conducted. A more potent sodium channel blocker, flecainide, can also be useful in severe forms of myotonia that are resistant to mexiletine [81]. However, it should be noted that long-term treatment of myotonia with sodium channel blockers is often limited by the side effects of the drugs.

Sodium Channelopathies of the Heart

In the heart, sodium channels are important for the ordered distribution of the action potentials from the sinoatrial node through the atria, the atrioventricular node, the His bundle through the specialized Purkinje conducting fibers to the ventricles (the His-Purkinje system), and further along the entire myocardium to stimulate rhythmic contraction. Mutations in the *SCN5A* gene encoding the main α-subunit expressed in the human heart cause hereditary predisposition to ventricular arrhythmia (congenital long QT syndrome, idiopathic ventricular fibrillation) [82], impaired cardiac conduction [83], or both diseases [84]. Mutations in *SCN5A* can also occur in the form of drug-induced arrhythmias [85], sudden infant death syndrome (SIDS) [86], and other forms of predisposition to arrhythmia [87].

Inherited arrhythmias: long QT syndrome and Brugada syndrome. Congenital long QT syndrome (LQTS) is a hereditary disease caused by abnormal repolarization of the myocardium and is characterized by a clinically increased risk of potentially fatal ventricular arrhythmias [88]. The syndrome is inherited most often in autosomal dominant families (Romano–Ward syndrome), but there are also families with autosomal recessive mode of inheritance in combination with congenital deafness (Jervell and Lange–Nielsen syndrome). The syndrome derives its name from the characteristic prolongation of the QT interval, revealed by electrocardiographic study of patients, which is a surrogate marker of increased duration of the action potential in the ventricles and abnormal repolarization of the myocardium. In approximately 10% of cases, LQTS is caused by mutations in the *SCN5A* gene, while the majority of patients with Romano–Ward syndrome have mutations in one of the two heart-specific potassium channel genes (*KCNQ1* and *HERG*) [89]. It is worth noting that factors which initiate the arrhythmia may be different in different genetic variants of LQTS, despite the fact that different mutations in *SCN5A* are often associated with different clinical signs, but all of them increase the risk of "large cardiac events" occurring during sleep or rest [90].

Mutations in the *SCN5A* gene were also described in patients with idiopathic ventricular fibrillation, including Brugada syndrome [91] and sudden unexplained death syndrome (SUDS) [92]. Individuals with Brugada syndrome have an increased risk of developing potentially lethal ventricular arrhythmias (polymorphic ventricular tachycardia or fibrillation) without concomitant ischemia, electrolyte disorders, or structural heart disease. Individuals with idiopathic ventricular fibrillation often display a characteristic ECG pattern consisting of an increase in the ST segment in the right chest leads, which is typical of the right bundle branch block, but with normal QT intervals [93]. The prescription of sodium channel blocking agents (for example, procainamide, flecainide, aymalin) in this condition can trigger similar pathological changes on ECG in a number of latent cases. Idiopathic ventricular fibrillation is inherited in an autosomal dominant manner with incomplete penetrance and is found predominantly in men. SUDS is a syndrome with a very similar clinical pattern, which leads to sudden death usually during sleep, and is described in young and middle-aged men in the Southeast Asian population [94].

Impaired cardiac conduction. Mutations in the *SCN5A* gene are also associated with heterogeneous hereditary cardiac conduction diseases, manifesting atrioventricular conduction disorders (heart block), decreased rate of intramyocardial conduction, or

atrial fibrillation [83]. The degree of cardiac conduction disorder may progress with age and is usually not associated with prolongation of the QT interval or other ECG changes corresponding to Brugada syndrome. Heart block in these states, as a rule, is a result of slowdown in the His-Purkinje system. In most cases, these conditions have the autosomal dominant type of inheritance. However, recessive disease, sick sinus syndrome, associated with mutations in the *SCN5A* gene [95] or having digenic inheritance of the heterozygous *SCN5A* mutation with a variant of the connexin-40 gene promoter [96], is described.

Sodium Channelopathies of the Peripheral Nerves

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system and can be divided into central and peripheral. Typical examples of neuropathic pain include postherpetic neuralgia, painful diabetic neuropathy, phantom limb pain, and pain arising from traumatic spinal cord injury. The main mechanism leading to the emergence of neuropathic pain is a lowering the threshold of nerve excitability, which manifests itself as a series of repetitive pulses, generated ectopically or with minimal stimulation. Damage to the nerve can lead to changes in the distribution of sodium channels on the surface of nerve cells, the expression of regulatory genes, and/or the electrical kinetics of the channel. All these contribute to the remodeling of the neuronal membrane and to hyperexcitability associated with neuropathic pain [97]. In the peripheral neurons and neurons of the dorsal root ganglion (DRG), $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ sodium channels, which appear to play an important role in the occurrence of neuropathic pain, were identified. Thus, these channels are new targets for anesthesia in peripheral neuropathic pain syndromes. In particular, $Na_V1.7$ is considered to be one of the main mediators of peripheral pain. In addition, it was recently showed in mouse model that the $Na_V1.8$ sodium channel is involved in molecular mechanisms that lead to the development of pain syndromes in osteoarthritis [98].

Inherited erythromelalgia, a chronic neuropathic pain syndrome, which is characterized by painful attacks in the limbs that begin in childhood and progress throughout life, is another peripheral sodium channelopathy. This disease is associated with mutations in *SCN9A*, resulting in hyperexcitability of the channel.

Congenital insensitivity to pain is characterized by a complete lack of perception of pain in patients with nonfunctional $Na_V1.7$. These patients also exhibit partial anosmia (loss of smell). In this case, nonsense mutations in *SCN9A* were identified.

CONCLUSIONS

Recent research elucidated the nature of many hereditary diseases of the nervous system. A significant group of diseases are now associated with the disruption of the voltage-gated sodium channel functioning. It seems that the study of the functional role of this group of channels may result in the development of new therapeutic agents.

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Translated by D. Novikova