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FUNCTIONAL ASPECTS OF SODIUM CHANNEL GENES (LOF, GOF) IN THE PATHOGENESIS OF EPILEPTIC ENCEPHALOPATHIES

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Abstract

Epileptic encephalopathies are severe neurodevelopmental disorders in the pathogenesis of which genetic factors play a key role, in particular mutations in the genes of voltage-gated sodium channels. This paper discusses the functional aspects of loss - of - function (LOF) and gain - of - function (GOF) mutations in the SCN family of genes (SCN 1 A, SCN 2 A, SCN 3 A, SCN 8 A) and their contribution to the development of epileptic encephalopathies. An analysis of current literature data on the molecular mechanisms of neuronal excitability disorders and their clinical manifestations is conducted. Particular attention is paid to the genotype-function-phenotype relationship and its significance for personalized therapy. It is shown that the functional characterization of mutations is important for the selection of an effective treatment strategy and disease prognosis.

Key words

epileptic encephalopathies, sodium channels, SCN 1 A, SCN 2 A, SCN 8 A, loss - of - function, gain - of - function, neuronal excitability, genetics, personalized medicine.

Abstract

Epileptic encephalopathies are severe neurodevelopmental disorders in which genetic factors, particularly mutations in voltage-gated sodium channel genes, play a crucial role. This study focuses on the functional aspects of loss-of-function (LOF) and gain-of-function (GOF) mutations in SCN gene family members (SCN1A, SCN2A, SCN3A, SCN8A) and their contribution to disease pathogenesis. A comprehensive review of recent literature was conducted to analyze molecular mechanisms underlying altered neuronal excitability and their clinical implications. Special emphasis is placed on the “genotype–function–phenotype” relationship and its importance for precision medicine. The findings highlight that functional characterization of mutations is essential for optimizing therapeutic strategies and improving clinical outcomes in patients with epileptic encephalopathies.

Keywords

epileptic encephalopathy, sodium channels, SCN1A, SCN2A, SCN8A, loss-of-function, gain-of-function, neuronal excitability, genetics, precision medicine.

Introduction. Epileptic encephalopathies (EEs) are a heterogeneous group of severe neurodevelopmental disorders characterized by early onset, drug-resistant seizures, and progressive cognitive deficits. In recent decades, advances in molecular genetics, including next-generation sequencing (NGS), have significantly expanded our understanding of the genetic basis of these disorders. One key area of research has been the study of voltage-gated sodium channel genes (SCN family), which play a central role in neuronal excitability. Voltage-gated sodium channels (Na_v) are transmembrane proteins that mediate the generation and propagation

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of action potentials in neurons. They consist of an α-subunit, encoded by SCN family genes (e.g., SCN1A, SCN2A, SCN3A, SCN8A), and accessory β-subunits. Dysfunction of these channels leads to an altered balance between excitation and inhibition in the central nervous system, which underlies palatogenesis. Of particular interest is the functional classification of mutations in sodium channel genes based on their effect on protein activity: loss-of-function (LOF) and gain-of-function (GOF). These two types of mutations result in different pathophysiological mechanisms and clinical phenotypes. LOF mutations typically result in decreased channel activity, while GOF mutations are accompanied by hyperactivity or impaired inactivation.

A classic example of a GOF-associated disorder is Dravet syndrome, caused by mutations in the SCN1A gene, which encodes the α-subunit of the $Na_v1.1$ channel. This channel is predominantly expressed in GABAergic interneurons, which mediate inhibitory regulation of neural networks. Loss of $Na_v1.1$ function leads to decreased inhibitory neuron activity and, consequently, hyperexcitability of neural networks and the development of seizures. Meanwhile, recent years have seen accumulating data on the role of GOF mutations in the pathogenesis of epileptic encephalopathies. For example, GOF variants in the SCN1A gene are associated with early forms of developmental and epileptic encephalopathy (DEE), characterized by an earlier onset and different clinical dynamics compared to classic Dravet syndrome. Furthermore, GOF mutations can alter the kinetics of channel activation and inactivation, enhancing the inward sodium current and increasing neuronal excitability. Importantly, the same gene can be associated with different phenotypes depending on the functional effect of the mutation. For example, SCN1A mutations can cause severe epileptic encephalopathy (LOF) as well as migraine with hemiplegia or early forms of EE (GOF). Similar functional variability is observed for other genes, such as SCN2A and SCN8A, where both LOF and GOF mutations can lead to a variety of neurological disorders, including epilepsy, autism, and movement disorders.

Current research highlights the importance of establishing the genotype-function-phenotype relationship, as clinical manifestations and response to therapy directly depend on the functional type of mutation. For example, in the case of LOF mutations in SCN1A, the use of sodium channel blockers can aggravate the disease, whereas in the case of GOF mutations, these drugs can be effective. This opens the prospect of personalized medicine based on the functional characterization of genetic variants. Despite significant progress, questions remain regarding the precise molecular mechanisms underlying the differences between LOF and GOF effects, as well as their interactions within complex neural networks. Moreover, cases of mixed mutations (GOF + LOF) have been described, further complicating the interpretation of clinical data and the choice of therapeutic strategy. Thus, studying the functional aspects of sodium channel gene mutations (LOF and GOF) is a key area of modern neurogenetics. Understanding these mechanisms not only deepens our knowledge of the pathogenesis of epileptic encephalopathies, but also facilitates the development of targeted therapies that target specific molecular defects.

Literature review. In recent years, there has been a rapid increase in the number of studies devoted to the role of voltage-gated sodium channel genes in the pathogenesis of epileptic encephalopathies (EE). The development of next-generation sequencing (NGS) technologies has made it possible to identify a wide range of mutations in genes of the SCN family, including SCN1A, SCN2A, SCN3A, SCN8A, and others, which has significantly expanded our understanding of the molecular mechanisms of these diseases (Helbig et al., 2018; Lindy et al., 2018). Modern research focuses not only on the identification of mutations but also on their functional interpretation within the framework of the loss-of-function (LOF) and gain-of-function (GOF) concepts. One of the best-studied genes is SCN1A, which encodes the α-subunit of the sodium channel $Na_v1.1$. Classic studies demonstrated that LOF mutations in this

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gene underlie Dravet syndrome, a severe form of early-onset epileptic encephalopathy (Claes et al., 2001; Catterall et al., 2010). Subsequent studies confirmed that loss of $Na_v1.1$ function primarily affects GABAergic interneurons, leading to impaired inhibitory transmission and hyperexcitability of neural networks (Yu et al., 2006; Ogiwara et al., 2007). However, more recent studies have shown that not all SCN1A mutations result in LOF effects. Thus, a number of studies in recent years have identified GOF variants associated with alternative phenotypes, including early forms of developmental and epileptic encephalopathy (DEE) and even non-epileptic disorders (Berecki et al., 2019; Brunklaus et al., 2020). These mutations alter the kinetics of channel inactivation, promoting increased sodium current and increased neuronal excitability. Thus, the functional heterogeneity of SCN1A mutations requires a more precise approach to their classification.

Studies of the SCN2A gene, which encodes the $Na_v1.2$ channel, have contributed significantly to our understanding of the role of GOF mutations. It has been established that GOF variants of SCN2A are more often associated with early-onset epileptic encephalopathies, while LOF mutations are associated predominantly with autism spectrum disorders and developmental delays without overt seizures (Sanders et al., 2018; Wolff et al., 2019). This underscores the importance of functional mutation analysis for predicting the clinical course of the disease. Similar patterns have been identified for the SCN8A gene, which encodes the $Na_v1.6$ channel, which plays a key role in initiating the action potential in the axonal initial segment. GOF mutations in SCN8A are associated with severe forms of EE, characterized by early onset and pharmacoresistance (Veeramah et al., 2012; Meisler et al., 2016). Functional studies have shown that such mutations lead to an increase in the persistent sodium current and impaired channel inactivation. At the same time, LOF variants of SCN8A are more often associated with milder neurological phenotypes, including intellectual disability without overt epilepsy (Wagnon et al., 2017). An important area of modern literature is the study of the SCN3A gene, which is expressed predominantly in the prenatal and early postnatal periods. GOF mutations in this gene are associated with cortical malformations and severe forms of epilepsy (Zaman et al., 2018). This indicates the role of sodium channels not only in the regulation of neuronal activity, but also in the processes of neuroontogenesis, including the migration and differentiation of neurons.

Current research actively utilizes electrophysiological methods (patch-clamp) and cellular models to assess the functional consequences of mutations. Such studies allow for a detailed study of changes in channel kinetics, including shifts in activation threshold, slower inactivation, and increased persistent current (Lossin, 2009; Catterall et al., 2020). Furthermore, the introduction of induced pluripotent stem cells (iPSCs) allows for modeling of patients' neural networks and the study of pathogenesis at the cellular level (Higurashi et al., 2013). Particular attention in the literature is given to therapies based on the functional classification of mutations. Sodium channel blockers (e.g., carbamazepine, phenytoin) have been shown to be effective against GOF mutations, whereas their use may worsen the condition of patients with LOF mutations, especially SCN1A (Brunklaus et al., 2012; Wirrell et al., 2017). This has become the basis for the development of the concept of precision medicine in epileptology.

In recent years, new therapeutic approaches have also been explored, including gene therapy, antisense oligonucleotides, and gene expression modifiers. For example, genetically engineered SCN1A expression enhancement has been shown to be effective in experimental models of Dravet syndrome (Colasante et al., 2020). These findings offer potential for the development of pathogenetically based treatments. Despite significant progress, controversial issues remain in the literature. In particular, it is not always possible to clearly assign a mutation to the LOF or GOF category, as some variants have mixed effects. Furthermore, the clinical

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phenotype may depend not only on the mutation type but also on its location in the protein and on interactions with other genetic and epigenetic factors (Meng et al., 2015). Thus, an analysis of the current literature demonstrates that the functional characterization of mutations in sodium channel genes is a key element in understanding the pathogenesis of epileptic encephalopathies. The LOF and GOF concept enable the integration of molecular, cellular and clinical data, creating the basis for a personalized approach to the diagnosis and treatment of these serious diseases.

Research results and discussion. The conducted analysis of the functional aspects of mutations in the sodium channel genes confirms the key role of disturbances in their activity in the pathogenesis of epileptic encephalopathies (EE). The obtained data are consistent with the current concept that the balance between excitation and inhibition processes in the central nervous system is a critical factor determining the development of epileptic activity. Disturbances in this balance, caused by loss-of-function (LOF) and gain-of-function (GOF) mutations, are realized through different but interconnected molecular mechanisms. In the framework of the present study, it was established that LOF mutations predominantly lead to a decrease in sodium channel activity, which, at first glance, should reduce neuronal excitability. However, in the case of genes expressed in inhibitory interneurons (e.g., SCN1A), a decrease in channel function leads to a weakening of GABAergic inhibition. This, in turn, causes a paradoxical increase in neuronal activity and the formation of hyperexcitability of neural networks. Thus, the LOF effect in this context is realized through dysfunction of the inhibitory system, which confirms the importance of cell specificity of gene expression.

Unlike LOF mutations, GOF mutations are characterized by increased channel activity, manifested by an increase in the amplitude or duration of the sodium current. Analysis results indicate that such changes may be associated with impaired channel inactivation, a shift in the activation threshold, or an increase in the persistent sodium current. This leads to facilitated action potential generation and an increased neuronal firing rate. A particularly pronounced effect of GOF mutations is observed in the SCN2A and SCN8A genes, which play an important role in excitatory neuronal circuits. Comparative analysis of LOF and GOF mutations shows that despite differences in their mechanisms, both types of changes lead to the same end result—disruption of the neuronal network and the development of epileptic activity. This suggests that the pathogenesis of EE should be considered not only at the level of individual ion channels but also in the context of complex neural networks. In particular, even local changes in the activity of individual neuronal populations can lead to systemic disturbances in brain function.

The functional ambiguity of mutations identified in a number of cases deserves special attention. Some variants exhibit mixed effects, combining features of LOF and GOF, making their classification difficult. This may be due to different experimental conditions, as well as the influence of the cellular context. For example, the same mutation may manifest itself differently depending on the neuron type, developmental stage, or the presence of modifying factors. Such observations highlight the need for a comprehensive approach to interpreting genetic data. The obtained results also have important clinical significance. It has been established that the functional type of mutation directly affects the effectiveness of antiepileptic therapy. In particular, in the case of GOF mutations, the use of sodium channel blockers can help reduce hyperexcitability and decrease seizure frequency. However, in the case of LOF mutations, especially those associated with SCN1A, such drugs can aggravate the clinical course of the disease. This confirms the need for functional diagnostics of mutations to select the optimal therapeutic strategy. Furthermore, the study results highlight the potential for the development of personalized treatments. The use of modern technologies, such as induced pluripotent stem cells

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(iPSCs) and gene editing, opens up opportunities for modeling diseases at the cellular level and developing targeted therapies. In particular, for LOF mutations, gene function restoration is a promising approach, while for GOF mutations, selective suppression of excessive channel activity is a promising approach.

However, a number of questions remain open. In particular, the mechanisms by which various mutations interact with each other, as well as their impact on the formation of neural networks during development, remain insufficiently studied. Furthermore, limited clinical data hinders the establishment of clear correlations between genotype and phenotype. This requires further research using multidisciplinary approaches integrating genetics, neurophysiology, and clinical neurology. Thus, this study confirms that LOF and GOF mutations in sodium channel genes play a key role in the pathogenesis of epileptic encephalopathies. Their functional characterization is an important tool for understanding disease mechanisms and developing effective treatments tailored to individual patient characteristics.

Conclusion. This study established that functional abnormalities in voltage-gated sodium channel genes play a key role in the pathogenesis of epileptic encephalopathies. Loss-of-function (LOF) and gain-of-function (GOF) mutations are realized through different molecular mechanisms but lead to a common result—an imbalance of excitation and inhibition in neural networks. LOF mutations, particularly in the SCN1A gene, contribute to a decrease in the activity of inhibitory interneurons, while GOF mutations enhance neuronal excitability by increasing the sodium current. It has been demonstrated that the functional classification of mutations has important clinical significance, as it determines the choice of effective therapy. The use of a personalized approach based on the analysis of the mutation type can improve treatment efficacy and reduce the risk of deterioration in patients' condition. Thus, further study of the functional effects of mutations in sodium channel genes is a promising direction for a deeper understanding of disease mechanisms and the development of targeted therapies.

References

1. Berecki, G., Howell, K. B., Deerasooriya, Y. H., Cilio, M. R., Oliva, M. K., Kaplan, D. I., ... & Petrou, S. (2019). Dynamic action potential clamp predicts functional separation in mild familial and severe de novo forms of SCN2A epilepsy. Proceedings of the National Academy of Sciences, 116(20), 10307–10316. https://doi.org/10.1073/pnas.1819754116
2. Brunklaus, A., Du, J., Steckler, F., Ghanty, I., Johannesen, K. M., Fenger, C. D., ... & Zuberi, S. M. (2020). Biological concepts in human sodium channel epilepsies and their relevance in clinical practice. Epilepsia, 61(3), 387–399. https://doi.org/10.1111/epi.16438
3. Brunklaus, A., Ellis, R., Reavey, E., Forbes, G. H., & Zuberi, S. M. (2012). Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain, 135(8), 2329–2336. https://doi.org/10.1093/brain/aws151
4. Catterall, W. A., Kalume, F., & Oakley, J. C. (2010). NaV1.1 channels and epilepsy. The Journal of Physiology, 588(11), 1849–1859. https://doi.org/10.1113/jphysiol.2010.187484
5. Catterall, W. A., Wisedchaisri, G., & Zheng, N. (2020). The chemical basis for electrical signaling. Nature Chemical Biology, 16(6), 619–627. https://doi.org/10.1038/s41589-020-0543-6
6. Claes, L., Del-Favero, J., Ceulemans, B., Lagae, L., Van Broeckhoven, C., & De Jonghe, P. (2001). De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. American Journal of Human Genetics, 68(6), 1327–1332. https://doi.org/10.1086/320609

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 6. No 04. Aprel ,2026

7. Helbig, I., Heinzen, E.L., Mefford, H.C., & International League Against Epilepsy Genetics Commission. (2018). Primer part 1—The building blocks of epilepsy genetics. Epilepsia, 59(4), 601–614. https://doi.org/10.1111/epi.14088
8. Higurashi, N., Uchida, T., Lossin, C., Misumi, Y., Okada, Y., Akamatsu, W., ... & Takahashi, J. (2013). A human Dravet syndrome model from patient induced pluripotent stem cells. Molecular Brain, 6(1), 19. https://doi.org/10.1186/1756-6606-6-19
9. Lossin, C. (2009). A catalog of SCN1A variants. Brain and Development, 31(2), 114–130. https://doi.org/10.1016/j.braindev.2008.07.011
10. Meisler, M. H., Hill, S. F., & Yu, W. (2016). Sodium channelopathies in neurodevelopmental disorders. Nature Reviews Neuroscience, 17(9), 595–608. https://doi.org/10.1038/nrn.2016.76