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Received 29 Oct 2025, Accepted 14 May 2026, Published online: 01 Jun 2026

JOURNAL OF RECEPTORS AND SIGNAL TRANSDUCTION
https://doi.org/10.1080/10799893.2026.2676552

Taylor & Francis
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REVIEW ARTICLE

Molecular insights into voltage-gated sodium channels in excitable cells: pathophysiological roles and emerging therapeutic targets

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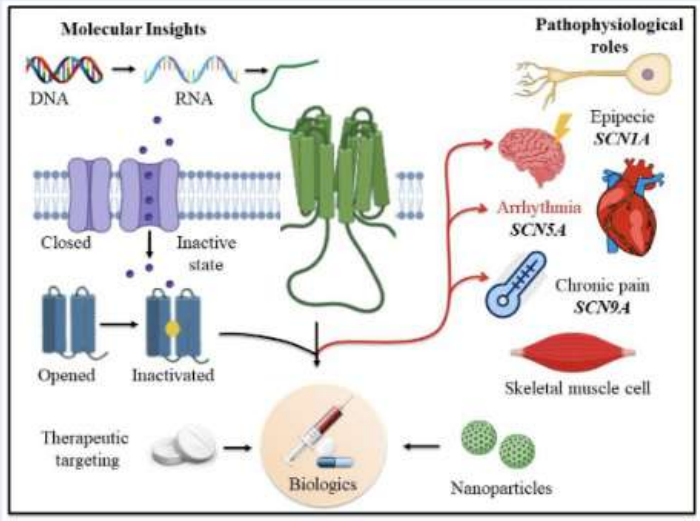
ABSTRACT

Voltage-gated sodium channels (VGSCs; Nav1.1–Nav1.9) are necessary for the initiation and propagation of action potentials in neurons, cardiac muscle and skeletal muscle. Because of their functional importance, VGSCs have become promising candidates for drug development in the brain, heart, and pain. The aim of this review is to highlight the structure, physiological role and pathological involvement of VGSCs in several different diseases, such as epilepsy, arrhythmias, chronic pain and cancer. Clinically established VGSC-targeting drugs are discussed, as well as recent evidence that shows an involvement of VGSCs in tumor progression and metastasis. Lack of selectivity, blood-brain barrier penetration, and regulatory complexities are among the challenges faced by VGSC-targeted therapy, as discussed in the review. Other challenges with VGSC-targeted therapy, such as high isoform homology, limited selectivity, blood–brain barrier penetration, and regulatory complexities, are also discussed in the review. In addition, new isoform-specific modulation strategies, innovative drug delivery devices, and new therapeutic approaches are highlighted. In summary, VGSCs are interesting but complex therapeutic targets, and future progress in selective targeting and drug delivery will likely increase their potential use across a variety of neurological, cardiovascular, and oncological disorders.

GRAPHICAL ABSTRACT

Overview of voltage-gated sodium channel showing structure, gating states, associated disorders (epilepsy, arrhythmia, chronic pain), and therapeutic approaches including drugs, biologics, and nanoparticles.



ARTICLE HISTORY
Received 29 October 2025
Revised 13 May 2026
Accepted 14 May 2026

KEYWORDS
Voltage-gated sodium channels (VGSCs); Nav; blood–brain barrier (BBB); CNS

Introduction

Voltage-gated sodium channels (VGSCs) are invaluable to the regulation of electrical excitability in neurons, cardiomyocytes, and muscle fibers. Despite the nine a-subunit isoforms of sodium channels (Nav1.1–Nav1.9) that have been successfully identified and studied, nonselective sodium channel blockers have been historically the basis of clinical pharmacology [1]. Although these agents have been used therapeutically for epilepsy, pain, and cardiac arrhythmias, they lack isoform selectivity and often cause dose-limiting

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