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EDITORIAL

Voltage-Gated Na Channels

Voltage-gated sodium channels: Mechanisms, disease, and a growing research community

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In this special issue of the *Journal of General Physiology* (*JGP*), we bring together a collection of studies that exemplify the multidimensional progress in physiology, pharmacology, and structure–function analysis of voltage-gated sodium (Na_V) channels. From computational studies and single-residue mutagenesis to insights into drug interactions and electrophysiological variability, the assembled papers illustrate the richness and continuing momentum of this field.

The history of modern physiology is closely linked to the study of bioelectricity, particularly the role of voltage-gated channels in generating action potentials (Hodgkin and Huxley, 1952). With each technological advance, researchers have gained a more detailed understanding of the genetic foundations, structures, and functions of sodium channels (Catterall, 2023).

We now recognize that nine *SCNA* genes encode the primary Na_V channel alpha subunits (Ahern et al., 2016). Initially, the exploration of Na_V channels was the domain of physiologists and biophysicists. However, the identification of these genes—especially the pathogenic variants in *SCNA* genes—has highlighted the significance of these channels in human diseases (Comini et al., 2024; Yamakawa et al., 2024; Vouloagkas et al., 2025).

Generations of scientists have dedicated their careers to studying Na_V channel biophysics, functionality, pharmacology, and, more recently, their structures. Increasingly, researchers are uncovering the roles these channels play in diseases, either due to pathogenic variants in the genes themselves or because the channels are integral to specific pathogenic pathways. Notably, the first disease-causing mutations were identified in the *SCN4A* gene in patients with periodic paralysis (Ptácek et al., 1991).

This special issue of *JGP* reflects the remarkable breadth and ongoing transformation of Na_V channel research (Fig. 1). Spanning from the deep structural biology of the cardiac $Na_V1.5$ channel to new pharmacological frontiers in pain signaling, these contributions capture both the sophistication and the complexity of Na_V channel biology.

The collection of articles reflects the current excitement in the field, with contributions that examine the structural and pharmacological basis of cardiac $Na_V1.5$ function—its fast inactivation mechanism, drug access pathways, and disease-causing mutations—reflecting its central role in cardiac excitability and arrhythmia. Additionally, pain-related channels $Na_V1.7$ and $Na_V1.8$ are explored in mechanistic and translational contexts, including drug profiling (e.g., suzetrigine and VX-548), toxin effects, and hyperexcitability in neuropathic states. This is not a new development, and *JGP* has been a major player in publishing Na_V-related research, which is reflected in several important publications over the past 2 or 3 years, e.g., on Structural and Biophysical Properties (Bertaud et al., 2024; Choudhury et al., 2023; Tikhonov and Zhorov, 2023), Pain and Neuroscience (Kriegeskorte et al., 2023; Wisedchaisri et al., 2023), Cardiac Sodium Channels (Lesage et al., 2023; Angsutararux et al., 2023; Weinberg, 2023), and Na_V Channel Regulation and Dysfunction (Gada et al., 2023; Thompson et al., 2023).

Methodologically, the special issue captures a spectrum of tools: experimental electrophysiology, computational modeling, including AlphaFold2 applications, cheminformatics, and theoretical approaches such as metaphor-driven conceptual reframing. There is also a growing focus on protein–protein interactions (e.g., β-subunit binding modulated by glycosylation) and a welcome openness toward complexity, such as the variability in inactivation kinetics across studies and conditions.

The Na_V channel communities have been meeting on numerous occasions, primarily in North America during the Biophysics annual meetings and the workshop organized by the

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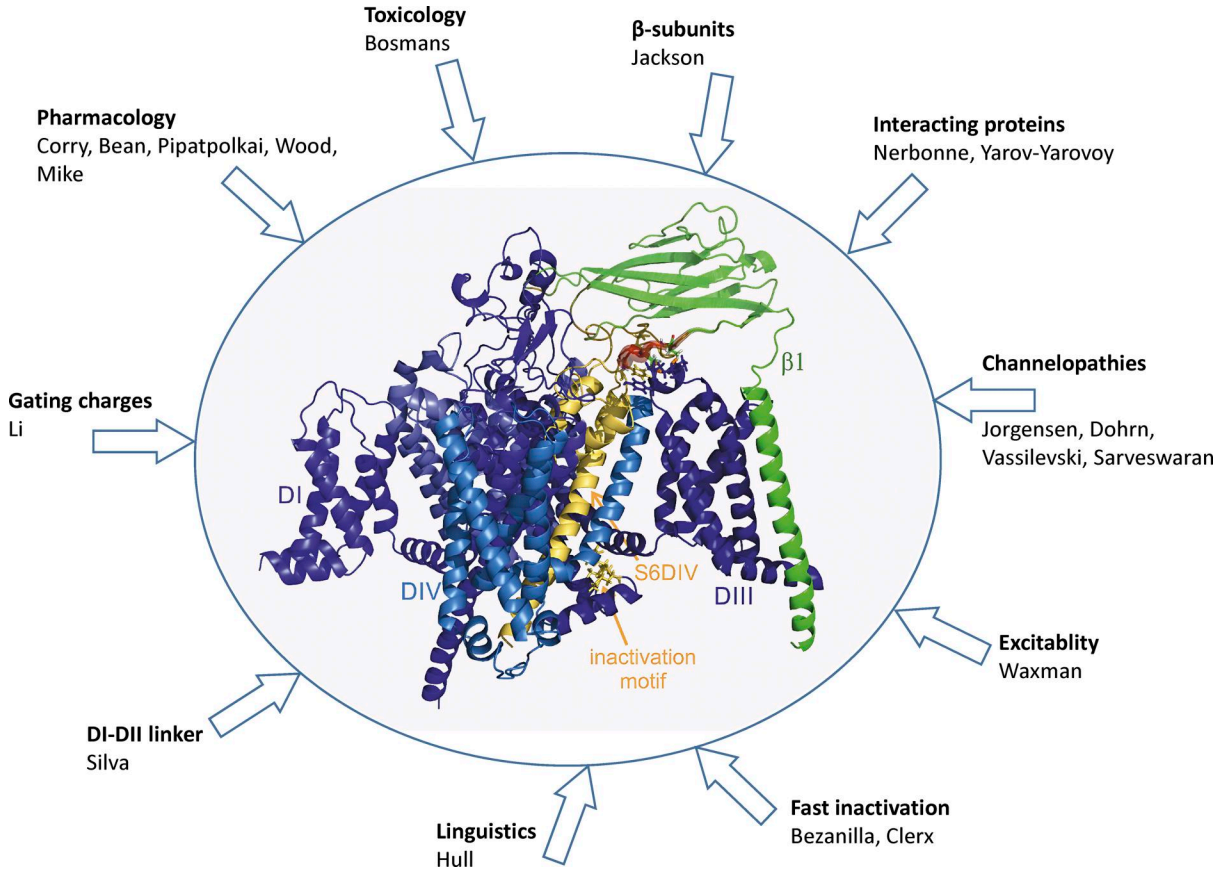

Figure 1. **Topics of publications in this special issue range from specific gating aspects, via pharmacology, interacting proteins, and subcellular localization, to effects on cellular excitability and channelopathies.**

Society of General Physiology in Woods Hole, MA, USA. The COVID-19 pandemic motivated these communities to connect in different ways, leading the authors of this editorial to launch a successful online Worldwide Sodium Channel seminar series (https://sodiumchannelseminars.org/Home/), with up to 200 participants per seminar. However, over time, we realized that a hybrid format that includes in-person meetings is the most effective approach to foster synergism and new ideas.

Together with our colleagues from Aachen (Germany) and Bern (Switzerland), we organized the inaugural Worldwide Sodium Channel Conference in Grindelwald in the Swiss Alps, where we used an innovative presentation format, allowing 10-min presentations for all participants independent of their scientific seniority (Pantazis and Brackenbury, 2024). *JGP* has been extremely generous in offering to publish this special issue related to this meeting. As this special issue appears, we are in the midst of planning the follow-up meeting, the second Worldwide Sodium Channel Conference (https://sodiumchannelconference2026.org/), which will also take place in Grindelwald in February 2026 and which will also be accompanied by a special issue in *JGP*. We look forward to all future interactions within the sodium channel community.

In summary, this special issue provides a cross section of the Na_V channel field at a particularly fruitful juncture. It reaffirms how Na_V channels continue to function as both clinical targets and windows into fundamental membrane physiology. We hope that these contributions stimulate further exploration—not only across isoforms but across experimental systems, methodological boundaries, and conceptual frames. We hope this collection serves as both a benchmark and a catalyst for these next steps in this exciting research field.

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