Ion Channels and Human Disease: A Review of Recent Research Advances

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Abstract: Ion channels are molecular structures located in the plasma membranes of cells as well as in certain non-cellular components of the human body, animals, and other organisms. These channels play a crucial role in numerous physiological processes across various functional systems of a healthy body, including the central and peripheral nervous systems, the heart, kidneys, lungs, gastrointestinal tract, and the immune system. Dysfunction or abnormal overexpression of ion channels in tissues and organs of these systems is often associated with a wide range of pathological conditions and diseases. Targeting these disease-related ion channels with specific pharmacological inhibitors has become a well-established and widely accepted approach in biomedical research. In some cases, treatment with ion channel inhibitors has demonstrated clinical benefit, and in many others, it is regarded as a promising strategy for therapeutic intervention in ion channel-related disorders. This mini-review provides a concise overview of recent research advances (from 2022 to 2025) focusing on the role of ion channels in disease pathogenesis, as well as the therapeutic potential of specific ion channel inhibitors for improving clinical outcomes in both experimental models and human patients.

***Keywords*:** ion channel, inhibitor, pathogenesis, therapeutics, purinergic receptor

Abbreviations:

AChEIs - acetylcholinesterase
AD - Alzheimer's disease
CAPs - channel-activating proteases
CFTR - cystic fibrosis transmembrane conductance regulator
CKD - chronic kidney disease
COPD - chronic obstructive respiratory diseases
Cx43 - Connexin 43
ENaC - epithelial sodium channel
HCC - Hepatocellular carcinoma
HF - heart failure
HFpEF - heart failure with preserved ejection fraction
IPF - Idiopathic pulmonary fibrosis
Kir - inwardly rectifying potassium channels
MI - myocardial infarction
NCX -sodium-calcium exchanger
NHE - sodium-hydrogen exchanger
NMDAR - N-methyl D-aspartate receptor
NO - endothelial nitric oxide
PKD - polycystic kidney disease
PP1 - serine/threonine protein phosphatase
RCC - refractory chronic cough
ROS - reactive oxygen species
RyR - ryanodine receptor

SERCA2a - SarcoEndoplasmic Reticulum Ca2+-ATPase
SGLT - Sodium-glucose cotransporter
SR - cardiac sarcoplasmic reticulum
TPC2 - lysosomal two-pore channel 2
TRP - transient receptor potential channel
TRPC - transient receptor potential canonical channel
TRPM7 - transient receptor ion channel of the subfamily M

Neurological disorders

In addition to the canonical potassium, sodium, and calcium ion channels that mediate central nervous system (CNS) function, other ion channels expressed in neural tissue are under active investigation. For example, the novel mechanosensitive ion channel Piezo1 plays a critical role in CNS physiology and pathology, particularly in neurological development and mechanosensory disorders (Xu et al., 2024). Piezo1 mediates Ca^{2+} transients essential for establishing vascular networks in the brain and contributes to the detection of capillary blood flow (Cudmore & Santana, 2022). Microinjection of the Piezo1 agonist Yoda1 into the basal forebrain—where Piezo1 is overexpressed—induces sleep deprivation and related phenotypes in mice (Ma et al., 2022). Comparable effects have also been observed in Piezo1 knockout models (Nourse et al., 2022). Recent studies indicate that Tubeimoside 1, a specific Piezo1 antagonist, competes with Yoda1 for the same binding site, supporting a Yoda1-dependent mechanism of action (Liu et al., 2020).

Neuronal excitability and pain transmission are closely linked to voltage-gated sodium channels, particularly Nav1.7, which is a promising therapeutic target for CNS disorders such as chronic pain, making it a key focus for the development of novel analgesics (Yu et al., 2024).

Gamma-glutamate is the primary excitatory neurotransmitter in the CNS. N-methyl-D-aspartate receptors (NMDARs)—glutamate-gated cation channels—are widely expressed in the brain and play a central role in excitatory synaptic transmission. Selective inhibition of NMDARs has been shown to confer resistance to chronic stress-induced depressive-like behaviors, highlighting their potential as targets for novel antidepressants such as (2R,6R)-hydroxynorketamine (Wang et al., 2024). In addition, non-competitive NMDAR antagonists (e.g., memantine) and acetylcholinesterase inhibitors (AChEIs) such as galantamine, donepezil, and rivastigmine are FDA-approved for the treatment of Alzheimer's disease (AD) (Puranik & Song, 2024).

Another important class of cation channels in the CNS is the transient receptor potential (TRP) channel family. These polymodal, non-selective cation channels act as biosensors that respond to a variety of mechanical and chemical stimuli—including stretch, extracellular ATP, and inflammatory mediators—making them promising therapeutic targets for neuropathic pain (Dangi & Sharma, 2024).

Finally, two-pore channel 2 (TPC2), which regulates intracellular calcium signaling, has been implicated in numerous pathological conditions. Recent advances in TPC2 structural biology, along with the development of specific agonists and inhibitors, have expanded understanding of its role in neurodegenerative diseases, cardiovascular conditions, inflammation, viral infections, and cancer (Alharbi & Parrington, 2025).

Cardiovascular Diseases

Protein phosphatases, particularly PP1, play a pivotal role in the regulation of cardiac function through their interactions with various cardiac ion channels and associated proteins, including Cav1.2, NKA, NCX, KCNQ1, RyR2, SERCA, PLB, MLC2, TnI, and MyBP-C. Dysregulation of PP1 and its regulatory subunits has been observed in multiple cardiac pathologies, making them promising therapeutic targets for the treatment of heart failure (HF) (Klapproth et al., 2022).

Pharmacological targeting of hyperactive RyR2 ion channels in the sarcoplasmic reticulum (SR) represents a compelling therapeutic strategy for cardiac arrhythmias and related cardiovascular disorders. Class II RyR2 inhibitors, such as dantrolene and Rycals, act by stabilizing the RyR2 channel in its closed state and are especially effective in structural heart diseases, where excessive Ca^{2+} leak from the SR impairs myocardial function. These agents reduce SR Ca^{2+} content and help restore myocardial contractility. By contrast, Class I RyR2 inhibitors (e.g., flecainide) suppress RyR2 "flickers" without eliciting compensatory increases in SR Ca^{2+}, making them particularly suitable for managing calcium-triggered arrhythmias, such as atrial fibrillation (AF) and catecholaminergic polymorphic ventricular tachycardia (CPVT) (Do & Knollmann, 2025).

The TRPC6 ion channel has been implicated in the pathogenesis of cardiac hypertrophy. Over the past decade, numerous natural, semi-synthetic, and synthetic modulators of TRPC6 activity have been explored as potential therapies for hypertrophy-associated cardiovascular diseases (Sharma et al., 2025).

SGLT2 inhibitors, originally developed as antidiabetic agents, have demonstrated profound cardiovascular benefits. Clinical trials, supported by *in vitro* and *in vivo* studies, show that these drugs reduce the incidence of cardiac arrhythmias, delay HF progression, and lower hospitalization and mortality rates (Attachaipanich et al., 2022; Wang et al., 2025). Consequently, SGLT2 inhibitors are now part of the standard therapeutic regimen for both heart failure and chronic kidney disease (CKD) (Wagner, 2025). Their beneficial effects are thought to involve modulation of the nitric oxide (NO) pathway, leading to reduced inflammation and reactive oxygen species (ROS) production in cardiac endothelial cells, as well as decreased intracellular Ca^{2+} levels through the inhibition of NHE1 and NCX (Wang et al., 2025).

Enhancement of SERCA2a activity and calcium reuptake has shown promise in animal models of HF, though its clinical translation remains uncertain. Several ongoing clinical trials are currently evaluating the efficacy of SERCA2a modulation in human heart failure patients (Shooshtarian et al., 2025).

The Piezo1 mechanosensitive ion channel has recently emerged as a critical player in HF pathogenesis. Targeting Piezo1 may represent a novel strategy for halting HF progression. A number of Piezo1-specific agonists and at least one selective antagonist are under investigation for their potential clinical application in cardiovascular diseases (Yuan et al., 2023).

Finally, gap junction proteins, including connexins and pannexins, contribute to cardiac electrophysiology and remodeling. A Cx43-targeting peptide, designed as a mimetic of the Cx43 carboxyl-terminal domain, has been shown to mitigate gap junction remodeling and reduce the incidence of cardiac arrhythmias (Marsh et al., 2022).

Renal Diseases

As previously mentioned, the Piezo1 ion channel is also highly expressed in the kidneys. Moreover, its expression is significantly upregulated during the pathogenesis of renal fibrosis. Two main classes of pharmacological agents have been explored for targeting this channel: (1) selective activators such as Yoda1 and Jedi1/2, and (2) non-selective inhibitors. Administration of these agents in animal models with induced renal fibrosis has been shown to modulate extracellular matrix deposition and improve kidney function (Drobnik et al., 2024).

Recent studies have also highlighted the critical roles of ciliary ion channels—including TRP channels, CFTR, and polycystins—in both normal renal cell signaling and the pathogenesis of polycystic kidney diseases (PKD1 and PKD2). Currently, therapeutic strategies involving TRPV4 activators and CFTR inhibitors are under investigation as innovative approaches to limit cyst growth and preserve renal function (Alshriem et al., 2025).

The transient receptor potential canonical 6 (TRPC6) channel is expressed in podocytes, and mutations in the TRPC6 gene have been linked to glomerulosclerosis—a progressive kidney disorder (Sharma et al., 2025).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, which block renal glucose reabsorption in the proximal tubules, have become standard therapy for patients with chronic kidney disease (CKD) (Mallamaci et al., 2020). In addition to SGLT2 blockade, inhibition of phosphate and amino acid transporters has recently been proposed as a strategy to provide metabolic protection to the proximal tubule (Wagner, 2025).

Apolipoprotein L1 (APOL1) G1 and G2 risk variants are strongly associated with increased susceptibility to kidney disease. Pharmacological inhibition of APOL1 channel activity is now being explored as a novel therapeutic strategy. Notably, SGLT2 inhibitors have demonstrated particular efficacy in the treatment of APOL1-associated kidney disease (APOL1-KD) (Pollak & Friedman, 2025; Afsar et al., 2025).

The voltage-gated potassium channel Kv1.3 plays a critical role in several physiological pathways. Inhibition of Kv1.3 has shown therapeutic benefit in multiple disease models. Emerging evidence supports a pathogenic link between Kv1.3 and CKD, highlighting this ion channel as a promising therapeutic target (Dragan et al., 2025).

It has been recently discovered that channel-activating proteases—CAP1 (prostasin), CAP2 (TMPRSS4), and CAP3 (matriptase)—act as *in vitro* mediators of ENaC currents. ENaC (epithelial sodium channel) is responsible for sodium reabsorption in the kidneys (**Figure 1**) and serves as a canonical example of ion channels. *In vivo* studies, particularly in knockout model animals, have provided evidence that CAPs enhance ENaC activity. This suggests that CAPs may serve as promising therapeutic targets for the treatment of renal dysfunctions related to sodium imbalance (Anand et al., 2022).

Respiratory Diseases

Specific inhibitors of the purinergic P2X3 receptor, a ligand-gated ion channel, have demonstrated promising antitussive effects in ongoing clinical trials involving patients with idiopathic pulmonary fibrosis (IPF) (Liu & Ye, 2023). Current research is also evaluating the efficacy of morphine sulfate, AX-8 (an agonist of the Transient Receptor Potential Melastatin 8 [TRPM8] channel), NTX1175, BW-031, and Orvepitant. A recently completed phase 2 trial of NAL-ER showed that its effects are both rapid and sustained (Ahluwalia et al., 2023). NAL-ER treatment has the potential to improve the quality of life in IPF patients by alleviating chronic cough (Liu & Ye, 2023).

TMEM16A (also known as anoctamin 1) is a calcium-activated chloride channel expressed in epithelial cells, smooth muscle cells, and certain neurons. Pharmacological modulation of TMEM16A may enhance mucociliary clearance in patients with chronic obstructive pulmonary disease (COPD). Inhibitors of TMEM16A also show potential as antihypertensive agents due to the channel's involvement in smooth muscle contraction (Genovese & Galietta, 2024).

Recent studies have further highlighted the therapeutic promise of targeting transient receptor potential (TRP) ion channels and purinergic receptors. These innovative approaches may improve the management of refractory chronic cough (RCC) by increasing drug efficacy, reducing side effects associated with current therapies, and expanding available treatment options (Guilleminault et al., 2024).

Interestingly, the M2 ion channel of the influenza A virus has emerged as a critical target for treating infections caused by both wild-type and drug-resistant strains. Recently developed compounds targeting this channel have shown promise in combating seasonal and resistant influenza (Kumar & Sakharam, 2024).

Immune Disorders

The novel mechanosensitive ion channel Piezo1 has been shown to induce the differentiation of macrophages into M1-like macrophages, which release pro-inflammatory factors (Solis et al., 2019). Activation of Piezo1 on dendritic cells similarly triggers the secretion of pro-inflammatory cytokines (Wang et al., 2022). Additionally, Piezo1 plays a regulatory role in T cell differentiation, influencing the balance between regulatory T cells (Tregs) and T helper 17 cells (Th17), thereby affecting immune homeostasis (Jairaman et al., 2021).

The TRPC6 channel is overexpressed in the macrophages of patients with chronic obstructive pulmonary disease (COPD) (Sharma et al., 2025). The TRPM7 channel is involved in both physiological and pathological immune responses, and accumulating evidence highlights its critical role in autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, and diabetes. TRPM7 has emerged as a promising therapeutic target for these conditions (Liang et al., 2022).

Kv1.3, a major voltage-gated potassium channel expressed in leukocytes of both the innate and adaptive immune systems, has been shown to play a key role in autoimmune and neuroinflammatory disorders. Inhibition of Kv1.3 has demonstrated beneficial therapeutic effects across several human diseases (Dragan et al., 2025; Navarro-Pérez et al., 2024). While multiple studies on ion channel modulation have shown promising results, only one specific Kv1.3 blocker has progressed to clinical trials. Nonetheless, future Kv1.3-based therapies hold the potential to deliver effective treatment while minimizing undesirable side effects (Navarro-Pérez et al., 2024).

Cancer Diseases

Among all areas of ion channel research, the investigation of ion channels in cancer and the development of specific ion channel inhibitors for cancer therapy is particularly prominent. Over the past three years, numerous studies have identified key ion channel targets in oncology, including TPC2 (Chi et al., 2024), various TRP family channels (Marini et al., 2023; Xu et al., 2024; Chinigò et al., 2024; Bai et al., 2023)—specifically TRPC6 (Sharma et al., 2025; Walker & Vuister, 2023), TRPV1 (Chinreddy et al., 2024), TRPV6 (Neuberger & Sobolevsky, 2023; Liu et al., 2024), and TRPM7 (Liu et al., 2023)—as well as Kv1.3 (Dragan et al., 2025; Cheng et al., 2024), KCa3.1 (Soret et al., 2022; Van et al., 2024), P2X7 (Li et al., 2023a; Yu et al., 2023; Du et al., 2024), TMEM16A (Li et al., 2023b), Orai1 (Mignen et al., 2024; Zhang et al., 2024), Nav1.7 (Yu et al., 2024), hERG1 (Arcangeli et al., 2024), and VGSCs (Bian et al., 2023). Several examples from recent literature are outlined below.

TPC2, a lysosome-localized ion channel, modulates intracellular calcium signaling pathways that are implicated in cancer pathogenesis. Inhibition of TPC2 has demonstrated therapeutic potential for cancer and viral infections. A novel TPC2 antagonist, SG-094, shows increased potency and reduced toxicity. SG-094 blocks the channel by arresting the IIS4 segment, preventing channel opening—an effect similar to inhibitors of voltage-gated ion channels. These findings support the development of new, TPC2-targeted anticancer drugs (Chi et al., 2024).

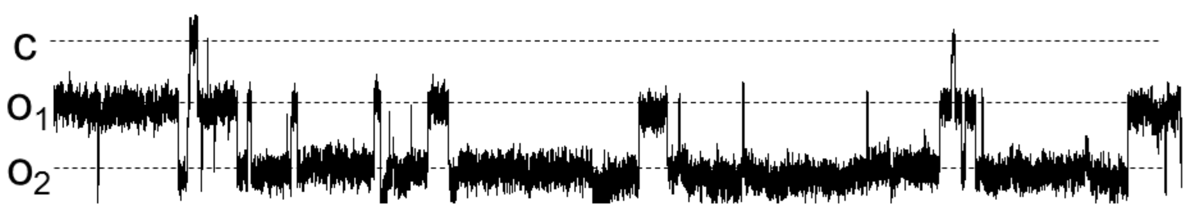
TRPC6 has been shown to contribute to the progression of several cancers, including breast, esophageal, renal, and head and neck squamous cell carcinoma (Sharma et al., 2025).

The Kv1.3 voltage-gated potassium channel is another important therapeutic target. Its inhibition has demonstrated beneficial effects in cancer treatment and in other disease models (Dragan et al., 2024).

The P2X7 purinergic receptor plays a role in hepatocellular carcinoma by promoting cell invasion and migration through the PI3K/AKT and AMPK signaling pathways. Both antagonists and inhibitors of P2X7 have been proposed as therapeutic agents for hepatocellular carcinoma and liver injury (Li et al., 2023a).

TMEM16A, a calcium-activated chloride channel, is physiologically important in various tissues but is abnormally expressed in many cancers. It has been linked to both carcinogenesis and metastasis (Li et al., 2023b). TMEM16A is now regarded as both a biomarker and a therapeutic target in cancer. Genetic knockdown or pharmacological inhibition of TMEM16A significantly suppresses tumor growth and provides anticancer effects (Li et al., 2023b).

Fig 1. Sample recording of the electrical activity (conductance) of two epithelial sodium channels (ENaCs). **C** indicates the closed state of both channels; **O1**, the open state of one channel; and **O2**, the open state of both channels.



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