The cGAS-STING Pathway, Ion Channel Dysregulation, and Immune Responses: Implications for Autoimmunity, Inflammation, Long COVID, and Post-Vaccination Responses

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Abstract

Ion channel dysfunction plays a pivotal role in neurological and autoimmune disorders, often leading to misdiagnoses due to symptom overlap with conditions like acute inflammatory demyelinating polyneuropathy, dysautonomia, postural orthostatic tachycardia syndrome (POTS), and small fiber neuropathy. This paper presents a theoretical framework linking ion channelopathies to autoimmunity through cGAS-STING pathway activation and macrophage polarization. It further explores how post-viral immune responses, including those in Long COVID and vaccine-related responses, may in rare instances, contribute to ion channel dysfunction, exacerbating autonomic and neuromuscular symptoms. The intersection of these mechanisms complicates diagnostic accuracy and therapeutic strategies. Sex-based differences and ethnic genetic predispositions in immune regulation are examined, offering insight into population-specific variations in immune-mediated ion channelopathies. This work highlights the need for improved diagnostic criteria and specific therapeutic interventions to address immune-driven ion channel dysfunction.

Keywords: ion channel dysfunction, autoimmune disorders, cGAS-STING pathway, macrophage activation, Long COVID, vaccine-related immune responses

Introduction

Ion channels are fundamental to neuronal excitability, immune regulation, and cellular homeostasis. Dysfunctions in these channels, whether driven by genetic mutations, autoimmunity, or environmental triggers, contribute to a constellation of neurological, immunological, and autonomic disorders. Aberrant ion channel activity alters macrophage polarization, inflammatory signaling, and neuroimmune interactions, leading to pathological hyperexcitability, immune dysregulation, and secondary mast cell activation. Mast cell activation, in turn, exacerbates inflammatory and neuroimmune responses, creating a feedback loop that worsens the clinical presentation (1).

Sex-based differences influence the severity of ion channelopathies, with women exhibiting greater susceptibility due to hormonal modulation of ion channel expression, immune hyperreactivity, and X-linked genetic predispositions (2,3). Additionally, variations in STING (stimulator of interferon genes) signaling between ethnic groups modulate immune responses to viral infections and inflammatory stimuli. European populations, particularly white Europeans, demonstrate heightened STING-related inflammatory activation, predisposing them to autoimmune and chronic inflammatory ion channel dysfunctions compared to African and Asian populations, who exhibit lower basal STING activity (4,5).

Despite the established role of ion channels in neuroimmune homeostasis, their contribution to misdiagnosed autoimmune and chronic inflammatory conditions remains underexplored. This review integrates evidence from molecular immunology, electrophysiology, and genetics to redefine the mechanistic role of ion channels in cGAS-STING-mediated immune dysfunction, vaccine-related inflammation, long COVID pathology, and mast cell activation (6).

1. Ion Channel Dysfunction: Symptoms, Mechanisms, and Genetic Factors

1.1 Symptoms

Ion channels are specialized membrane proteins that facilitate the selective passage of ions across cellular membranes, which cellular homeostasis. These channels help regulate electrical excitability, signal transduction, and cellular communication across nearly all cell types, including neurons, muscle cells, and immune cells. By controlling the flow of key ions like sodium, potassium, calcium, and chloride, ion channels control processes critical for physiological functions like nerve impulse transmission, muscle contraction, and immune response modulation. In immune cells, ion channels influence activation, migration, and cytokine production, influencing the body's defense mechanisms. Disruptions in ion channel function, due to genetic mutations and ion channelopathies, may cause several pathologies, including neurological disorders, cardiac arrhythmia, and immune dysregulation (7).

Ion channelopathies encompass a constellation of disorders resulting from dysfunctional ion channels, leading to various clinical manifestations. Patients often experience chronic pain characterized by sensations including burning, stabbing, or electric shock-like feelings. Dysautonomia is another common feature, presenting with symptoms like tachycardia, gastrointestinal dysmotility, and orthostatic intolerance. Neuromuscular weakness is frequently observed, particularly in conditions like Lambert-Eaton myasthenic syndrome, where autoantibodies target voltage-gated calcium channels at the neuromuscular junction. Sensory disturbances, including hyperesthesia, paresthesia, and allodynia, are also prevalent, reflecting altered sensory neuron excitability due to ion channel mutations (8,2)

Women often report more severe autonomic dysfunctions in channelopathies. This disparity may be influenced by estrogen's modulation of ion channel expression and function, affecting autonomic control mechanisms. Estrogen has been shown to modulate nociception by altering ion channel opening and regulation of receptor expression in peripheral visceral afferent terminals. Estrogen can modulate the function of RVLM C1 bulbospinal neurons either directly, through extranuclear estrogen receptor beta, or indirectly through other mechanisms (3,4).

1.2 Genetic Mutations and Ion Channelopathies

Voltage-gated sodium channels are essential for the initiation and propagation of action potentials in excitable tissues. Mutations in the genes encoding these channels, like SCN9A (Nav1.7), SCN10A (Nav1.8), and SCN11A (Nav1.9), have been implicated in various pain syndromes (9).

SCN9A encodes the Nav1.7 channel, primarily expressed in nociceptive neurons. Gain-of-function mutations in SCN9A lead to conditions like inherited erythromelalgia and paroxysmal extreme pain disorder by lowering the activation threshold of Nav1.7, resulting in neuronal hyperexcitability and spontaneous pain. Loss-of-function mutations cause congenital insensitivity to pain relative to Nav1.7's role in nociception (10).

SCN10A encodes Nav1.8, a tetrodotoxin-resistant sodium channel integral to action potential upstroke in peripheral nociceptors. Mutations in SCN10A have been associated with painful neuropathies by enhancing neuronal excitability by altering channel inactivation and recovery kinetics (11).

SCN11A encodes Nav1.9, another tetrodotoxin-resistant sodium channel expressed in nociceptors. Gain-of-function mutations in SCN11A are linked to familial episodic pain syndrome, characterized by severe limb pain due to increased persistent sodium currents and neuronal hyperexcitability. Specific mutations in SCN11A increase insensitivity to pain (12).

Voltage-gated potassium channels (Kv) are crucial for repolarizing the neuronal membrane following action potentials. Mutations in KCNA1, encoding the Kv1.1 channel, are associated with episodic ataxia type 1 (EA1) and neuromyotonia which impair Kv1.1 function, leading to neuronal hyperexcitability and the clinical manifestations of EA1 (13).

Calcium channels encoded by CACNA1A influence neurotransmitter release and neuronal excitability. Mutations in CACNA1A result in conditions like familial hemiplegic migraine and episodic ataxia type 2 by altering calcium influx, disrupting synaptic transmission and leading to the clinical features observed in these disorders. Estrogen can modulate calcium channel function, influencing the higher prevalence of migraine in women (14).

Chloride channels, like those encoded by CLCN1, maintain skeletal muscle excitability. Mutations in CLCN1 cause myotonia congenita, driving impaired muscle relaxation due to reduced chloride conductance and subsequent muscle hyperexcitability (15).

1.3 Ion Channel Mutations and Population Prevalence

Genetic variants affecting ion channel function are widespread in the human population, with many exhibiting functional consequences that influence neuronal excitability, pain perception, and immune regulation. Variants in voltage-gated sodium channels, such as SCN9A (Nav1.7), SCN10A (Nav1.8), and SCN11A (Nav1.9), are implicated in inherited pain disorders, including erythromelalgia and small fiber neuropathy, with pathogenic mutations occurring in approximately 1 in 1,000 to 1 in 10,000 individuals (16,17). Loss-of-function mutations in SCN9A can lead to congenital insensitivity to pain, while gain-of-function mutations enhance nociceptor excitability, predisposing individuals to chronic pain syndromes (18).

Voltage-gated potassium channels, particularly KCNA1 (Kv1.1), KCNQ2 (Kv7.2), and KCNQ3 (Kv7.3), regulate neuronal repolarization and excitability. Mutations in KCNA1 are linked to

episodic ataxia type 1, with a prevalence estimated at 1 in 100,000 (19). KCNQ2 and KCNQ3 mutations driving neonatal epilepsy syndromes, affecting ~1 in 25,000 newborns (20).

Voltage-gated calcium channels, such as CACNA1A, CACNA1C, and CACNA1S, influence synaptic transmission and muscle contraction. CACNA1A mutations are associated with familial hemiplegic migraine and episodic ataxia type 2, with a combined prevalence of 1 in 50,000 (Jen et al., 2001). Mutations in CACNA1C contribute to Timothy syndrome, a rare disorder affecting cardiac and neurological function, with an incidence of fewer than 1 in 1 million (21).

Chloride channelopathies, including CLCN1 mutations linked to myotonia congenita, are more common, with Thomsen and Becker myotonia occurring in 1 in 100,000 to 1 in 50,000 individuals, respectively (22).

2. Autoimmunity and Ion Channels

2.1 cGAS-STING Activation

The cGAS-STING pathway detects cytosolic DNA, viruses, and bacteria--triggering innate immune responses through the production of type I interferons and pro-inflammatory cytokines. While paramount for pathogen defense, dysregulated cGAS-STING activation can contribute to autoimmune diseases and chronic inflammation (23). Activation occurs when cGAS detects cytosolic double-stranded DNA and specific pathogens, producing cyclic GMP-AMP (cGAMP), which activates STING and induces the release of type I interferons like IFN-α, IFN-β and inflammatory cytokines. The persistent activation of this pathway can lead to prolonged inflammation, autoimmune responses, and tissue damage (24).

In autoimmune diseases like Guillain-Barré syndrome (GBS) and Acute Inflammatory Demyelinating Polyneuropathy (AIDP), the immune system mistakenly targets peripheral nerves, causing inflammation and demyelination (25). Dysregulated cGAS-STING activation can perpetuate this immune response (26). Exogenous DNA fragments from environmental or other sources may persist in tissues, continuously triggering cGAS-STING and exacerbating inflammation (27). Molecular mimicry, where the immune system targets self-DNA due to similarities with foreign DNA, nuclear DNA, viral DNA, and mitochondrial DNA--can further sustain autoimmune damage via cGAS STING pathway activation (28).

Type I interferons bind to their receptors (IFNAR1/2), activating transcription factors like STAT1 and STAT2. These factors form the ISGF3 complex, which translocates to the nucleus and induces the expression of interferon-stimulated genes (ISGs) (29). Some ISGs enhance cGAS-STING signaling, establishing a positive feedback loop that amplifies immune responses and inflammation, promoting excessive and sometimes continuous neuroinflammation and neurodegeneration in autoimmune conditions (30).

Chronic cGAS-STING activation in the peripheral nervous system (PNS) results in neuroinflammation, characterized by immune cell infiltration and the release of inflammatory mediators (31). This exacerbates demyelination and neuronal injury, contributing to disease progression in AIDP and other neuroinflammatory disorders (32).

Mutations in genes involved in cGAS-STING or related immune pathways potentially influence susceptibility to autoimmune diseases (33). Environmental factors, like microbial DNA or contaminants, can reinforce ongoing cGAS-STING activation, leading to persistent inflammation and immune dysregulation (33).

2.2 Macrophage Activation, Ion Channels, and Immune System Crosstalk

Macrophages, central mediators of both innate immunity and tissue homeostasis, undergo dynamic polarization in response to a variety of signals. These signals, including cytokines, danger-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), and even external physical cues like electrostatic forces, dictate whether macrophages adopt a pro-inflammatory M1 phenotype or an anti-inflammatory M2 phenotype (34). Physical properties like zeta potential, the electrostatic charge of particles, and charged particles like lipid interactions are found to influence macrophage polarization (35), especially in the context of nanoparticles (NPs) and lipid-based nanocarriers (LNPs) used in drug delivery systems (36).

Zeta potential refers to the electrostatic potential at the interface between a particle and the surrounding fluid, which is a measure of the particle's surface charge (37). This charge can influence cellular interactions, including those with macrophages. When nanoparticles NPs or LNPs meet macrophages, their surface charge can modulate the macrophage's ability to recognize, internalize, and subsequently polarize in a pro-inflammatory or anti-inflammatory state (38).

Positively charged nanoparticles have been shown to preferentially interact with the negatively charged components of the macrophage cell membrane (39). The interaction of cationic particles with macrophage membranes can in rare instances, induce cellular stress and inflammation, triggering the macrophage to adopt a pro-inflammatory M1 phenotype. This process is facilitated by the recognition of charged nanoparticles via surface receptors, like scavenger receptors, which are involved in the uptake of damaged or altered particles (39). The uptake of cationic particles activates intracellular signaling pathways, notably the NF-κB and MAPK pathways, which are critical for the transcription of pro-inflammatory cytokines like IL-6, TNF-α, and IL-1β (40). These cytokines, in turn, not only exacerbate local tissue inflammation but also amplify systemic immune responses, which could potentiate autoimmunity or contribute to chronic inflammatory diseases (41).

The electrostatic interaction between the positively charged lipids and the macrophage membrane increases the likelihood of membrane disruption and phagocytic uptake, promoting the secretion of cytokines and reactive oxygen species (ROS) that contribute to tissue damage and inflammation (42).

Negatively charged particles can promote macrophage polarization toward an M2 phenotype, which are associated with immune suppression, tissue repair, and resolution of inflammation (44). The binding of negatively charged particles to macrophage scavenger receptors or CD36 can enhance the macrophage's capacity to clear apoptotic cells and induce cytokine production that promotes tissue healing, rather than inflammation (45). Thus, the surface charge of particles

can provide a significant determinant of macrophage phenotype and immune response.
The exposure of macrophages to various cytokines and growth factors plays a dominant role in determining their polarization. The presence of interferon-gamma (IFN-γ) and lipopolysaccharide (LPS) drives macrophages toward the M1 phenotype, characterized by the production of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6, as well as reactive nitrogen species (RNS) and ROS (46). On the other hand, anti-inflammatory cytokines including IL-4, IL-10, and transforming growth factor-beta (TGF-β) promote M2 polarization, marked by increased expression of markers like CD206 and arginase-1, and the production of cytokines like IL-10 and TGF-β that promote tissue repair and immune resolution (47).

Macrophage polarization is also heavily influenced by changes in cellular metabolism. M1 macrophages typically undergo a shift toward glycolytic metabolism to meet the high energy demands associated with their inflammatory activity (48). This metabolic reprogramming is regulated by transcription factors like HIF-1α and c-MYC, which drive the expression of glycolytic enzymes (48). In contrast, M2 macrophages rely more on oxidative metabolism and fatty acid oxidation, processes associated with their role in tissue repair and immune modulation. This metabolic shift is not only a marker of macrophage polarization but also a key regulator of their functional properties in inflammation and immunity (48).

MicroRNAs (miRNAs) have been implicated in macrophage polarization. Specific miRNAs, like miR-155, promote M1 polarization by enhancing the expression of inflammatory cytokines and boosting the activation of signaling pathways like NF-κB (49). Conversely, miR-124 and miR-147 have been shown to drive M2 polarization by suppressing pro-inflammatory pathways and promoting the anti-inflammatory phenotype (50).

The local tissue microenvironment also plays a critical role in macrophage polarization. Hypoxic conditions, found in inflamed or injured tissues, can induce a shift toward M2 polarization, facilitating tissue repair and immune resolution. This is largely mediated through the stabilization of hypoxia-inducible factors (HIFs), particularly HIF-1α, which orchestrates the transcription of genes involved in metabolic adaptation, angiogenesis, and immune modulation (51).

Gender differences in immune responses, particularly the stronger macrophage activation observed in women, have been well-documented. Estrogen, through its receptors (ERα and ERβ), plays a crucial role in modulating macrophage function (53), influencing both polarization and cytokine production. In women, estrogen enhances macrophage responsiveness to inflammatory signals, leading to a more robust M1 response. The increased M1 response can result in increased production of pro-inflammatory cytokines like IL-6 and TNF-α, which are associated with autoimmune diseases like multiple sclerosis, rheumatoid arthritis, and autoimmune encephalitis (53). Estrogen also affects the expression of ion channels in immune cells, further contributing to the gender differences observed in autoimmune ion channel disorders (54).

The polarization of macrophages, particularly in the context of nanoparticle exposure and charge-based interactions, has significant implications for autoimmune ion channel disorders (55). These disorders, in which the immune system targets ion channels, are exacerbated by the inflammatory environment created by M1 macrophages (56). The production of cytokines like

IL-6 and TNF-α can enhance the activation of autoreactive T cells and B cells, promoting the production of autoantibodies against ion channels (57).
Macrophage polarization is a multifaceted process influenced by both biochemical and physical factors. Zeta potential, particularly through charge-based interactions with nanoparticles, represents an underexplored but important mechanism in macrophage polarization. The charge and surface properties of particles like LNPs may modulate macrophage function, contributing to either a pro-inflammatory M1 or anti-inflammatory M2 phenotype, highlighting the complexities of autoimmune diseases, especially autoimmune ion channel
disorders.

2.3 Autoantibodies and Ion Channels

The production of autoantibodies targeting ion channels plays a pivotal role in the pathogenesis of several autoimmune neurological disorders, including Morvan's syndrome and autoimmune encephalitis (58). These conditions are characterized by the development of autoantibodies against specific neuronal ion channels, like voltage-gated potassium channels (VGKC), Contactin-associated protein-like 2 (CASPR2), and Leucine-rich glioma-inactivated 1 (LGI1). These autoantibodies disrupt normal neuronal function, contributing to severe and often debilitating symptoms, like seizures, memory deficits, and dysautonomia (59).

VGKC autoantibodies appear in Morvan's syndrome--the antibodies specifically target the extracellular domains of VGKCs (59). This disrupts the normal function of these channels in neurons, affecting potassium ion homeostasis and altering neuronal excitability. Potassium channels are crucial for regulating potential propagation and neurotransmitter release—the loss of proper VGKC function leads to the hyperexcitability of neurons (60), manifesting as symptoms like myokymia, seizures, and cognitive impairment (61).

CASPR2 and LGI1 are also critical targets in autoimmune encephalitis (62). CASPR2, a cell adhesion molecule involved in the clustering of voltage-gated potassium channels at the nodes of Ranvier, maintains the integrity of the nodes and ensures proper saltatory conduction in myelinated fibers. Autoantibodies targeting CASPR2 disrupt this process, leading to demyelination and neuronal dysfunction (62).

Autoantibodies against LGI1, a protein that regulates synaptic transmission, interferes with synaptic plasticity and neuronal signaling, contributing to the cognitive and psychiatric symptoms associated with autoimmune encephalitis (62).

A notable feature of autoimmune ion channel disorders is the gender disparity in disease prevalence and severity. Women, particularly during their reproductive years, exhibit higher levels of autoantibody titers and experience more severe neurological symptoms compared to men. This is primarily driven by the influence of estrogen on immune regulation. Estrogen enhances B cell activation and antibody production, promoting a more robust autoimmune response in women (63). Estrogen's effect on macrophage polarization, as discussed earlier, also contributes to the heightened immune response seen in women, amplifying the production of pro-inflammatory cytokines and potentially increasing the production of ion channel-targeting autoantibodies, including impacts on ovarian cancer (64).

Estrogen interacts with estrogen receptors (ERα and ERβ) on immune cells, including B cells and macrophages, to regulate key pathways involved in autoimmunity (54). By binding on these receptors, estrogen enhances the differentiation and activation of B cells, leading to increased autoantibody production. Estrogen modulates the Th1/Th17 balance in favor of pro-inflammatory responses, further exacerbating the autoimmune attack on neuronal ion channels resulting in a higher incidence of disorders (53) like autoimmune encephalitis, where autoantibodies direct themselves against neuronal ion channels like VGKC, CASPR2, and LGI1 (62).

Estrogen's role in modulating the blood-brain barrier (BBB) can also influence the infiltration of immune cells into the CNS, contributing to the severity of disease. Studies have shown that estrogen increases the permeability of the BBB, making it easier for auto-reactive immune cells, including T cells and B cells, to enter the CNS and target neuronal structures, including ion channels (65).

The binding of autoantibodies to ion channels in the CNS leads to a cascade of pathophysiological events. With VGKC, CASPR2, and LGI1, autoantibody binding interferes with channel function, causing neuronal hyperexcitability, disrupted synaptic transmission, and altered ion gradients resulting in clinical manifestations of autoimmune encephalitis, including seizures, cognitive dysfunction, psychiatric disturbances, and autonomic dysregulation (66).

The disruption of potassium channels in neurons, impairs repolarization following action potentials, thereby prolonging depolarization and enhancing neuronal excitability. This hyperexcitability is a hallmark of several autoimmune neurological disorders—contributing the generation of spontaneous seizures and the onset of neurological deficits. CASPR2 and LGI1 autoantibodies may disrupt neuronal communication, affecting both synaptic and non-synaptic signaling. The resultant neuronal dysfunction can lead to a range of cognitive and behavioral symptoms, like memory loss, confusion, and even psychosis (67)..

The inflammatory milieu generated by the heightened immune response exacerbates neuronal injury by activating macrophages and microglia, creating an environment of chronic inflammation in the central nervous system progressing neuronal damage (68).

3. Diagnostic Challenges and Misdiagnosis

3.1 Acute Inflammatory Demyelinating Polyneuropathy and Small Fiber Neuropathy

Acute inflammatory demyelinating polyneuropathy (AIDP), small fiber neuropathy (SFN), and ion channelopathies present complex diagnostic challenges due to overlapping clinical symptoms, shared pathophysiological features, and differential responses to treatment (8). These disorders represent diverse etiologies of peripheral nerve dysfunction, yet frequently manifesting with similar neurological symptoms, like pain, sensory disturbances, autonomic dysfunction, and motor weakness. The intricate molecular mechanisms underlying these conditions, with limitations of current diagnostic technologies, contribute to the frequent misdiagnosis of these disorders—resulting in delayed or inappropriate treatment.

AIDP, a subset of Guillain-Barré Syndrome (GBS), is characterized by immune-mediated demyelination of peripheral nerves involving the Schwann cells and myelin sheath. The pathological hallmark of AIDP is the invasion of autoimmune T lymphocytes and macrophages into peripheral nerves, resulting in demyelination, axonal injury, and uncommonly, axonal loss. Clinically, AIDP presents rapid onset ascending muscle weakness, paresthesia, and autonomic dysfunction like tachycardia, hypotension, and gastrointestinal disturbance (69).

Molecularly, AIDP develops through the activation of autoreactive T cells. The CD4+ T helper cells initiate the immune response, while CD8+ cytotoxic T cells contribute to direct tissue damage through cytokine release and cytolysis (70). These T cells are activated by myelin-associated antigens, like GM1 gangliosides or myelin basic protein, triggering an inflammatory cascade that destroys the myelin sheath (71). As the inflammatory process progresses, macrophages infiltrate the demyelinated areas, exacerbating axonal damage through the secretion of pro-inflammatory cytokines like TNF-α, IL-6, and IFN-γ and reactive oxygen species (72).

Diagnostic confirmation of AIDP is often achieved through cerebrospinal fluid (CSF) analysis, searching for elevated protein levels (albumin cytologic dissociation) without a corresponding increase in white blood cells. Nerve conduction studies may show delayed motor and sensory conduction velocities, reflecting demyelination. However, AIDP diagnosis can be confounded by similar symptoms in other neuroimmune disorders, particularly when electrophysiological findings are borderline or when there is a lack of detectable antibodies (73).

Small fiber neuropathy SFN is another condition with overlapping features that often complicate the diagnosis of AIDP and other neuropathies (75). SFN primarily affects the small myelinated Aδ fibers and unmyelinated C fibers of peripheral nerves, which are involved in nociception and autonomic regulation. Unlike AIDP, SFN does not typically involve large, myelinated fibers, which are essential for motor and proprioceptive functions, making the diagnosis of SFN more elusive in the early stages (76). Symptoms of SFN are often disabling, including chronic pain, burning sensations, paresthesia, and autonomic dysfunction like orthostatic hypotension, tachycardia, sweating abnormalities, and gastrointestinal disturbances (74). From a pathophysiological perspective, SFN results from the degeneration of small fiber axons, often due to a variety of underlying causes, including autoimmune diseases, genetic mutations, infections, and diabetes mellitus (74).

3.2 AIDP, SFN, and Ion channelopathies

Ion channelopathies are a class of disorders caused by genetic mutations or autoimmune responses that alter the normal functioning of ion channels, which are integral to maintaining neuronal excitability and synaptic transmission (77). These conditions are often overlooked in clinical practice. Ion channelopathies encompass a wide range of conditions, including epilepsy, migraines, and neuromuscular disorders, autoimmune channelopathies, and cardiac channelopathy (77).

The pathophysiology of ion channelopathies is diverse, involving disrupted ion flow due to mutations or autoimmune antibodies (78) that target critical components of ion channels or their

associated proteins. VGKC autoantibodies target extracellular epitopes of the potassium channels, leading to disrupted potassium ion flux, which in turn alters neuronal repolarization and action potential propagation. This disruption of neural signaling is a hallmark of autoimmune neuromyotonia, which presents symptoms like muscle spasms, ataxia, seizures, and cognitive dysfunction. Similarly, CASPR2 and LGI1 autoantibodies interfere with the clustering of ion channels at the nodes of Ranvier, contributing to the demyelination and neuronal dysfunction seen in autoimmune encephalitis (79).

Autoimmune SFN research has highlighted the potential role of autoantibodies targeting ion channels in the pathogenesis of SFN. Voltage-gated sodium channels (NaV1.7) have been implicated in some cases of immune-mediated SFN, where autoantibodies alter the function of ion channels, leading to disrupted neuronal excitability, pain hypersensitivity, and autonomic disturbances (80). Despite these insights, electrophysiological studies in SFN remain normal or only mildly altered (81), further complicating the diagnosis and distinguishing it from other similar conditions like AIDP.

The diagnostic challenge in ion channelopathies lies in the absence of clear-cut electrophysiological findings and the normal appearance of brain and nerve imaging. Conventional tests, including nerve conduction studies and electromyography, may fail to reveal the underlying ion channel dysfunction. As a result, serological testing for autoantibodies directed against specific ion channel proteins, like CASPR2, or LGI1, is increasingly recommended to confirm these conditions 82). Magnetic resonance imaging may show brain atrophy or hippocampal abnormalities in cases of autoimmune encephalitis, but it lacks sensitivity for detecting the subtle functional changes that underline these disorders (83).

3.3 Current Testing Limitations

Despite advancements in diagnostic technologies, distinguishing between SFN, autoimmune diseases, and ion channelopathies remains challenging due to limitations in current testing methods (84). These challenges often result in missed or delayed diagnoses, complicating patient management (84).

Skin biopsy, commonly used to diagnose SFN, allows examination of small nerve fibers in the epidermis, but lacks sensitivity to identify the underlying etiology (85). It cannot distinguish between autoimmune and genetic causes of small fiber degeneration (86). Autoimmune SFN, driven by autoantibodies against ion channels like NaV1.7 or TRPV1, and genetic SFN with mutations in ion channels or structural proteins, can present similarly (87). Variability in epidermal nerve fiber density (ENFD) cutoffs across labs contributes to inconsistent results (88).

Autoantibody panels are critical for diagnosing autoimmune-mediated neuropathies, especially ion channelopathies (89), but often miss key auto antibodies against neuronal ion channels like VGKC, CASPR2, LGI1, and NaV1.7 (90). Sensitivity varies between labs, and narrow panel selection may overlook less common or newly identified antibodies [Dale et al., 2012]. Cross-reactivity with non-specific proteins can complicate the diagnostic process (92).

In autoimmune SFN and conditions like Morvan’s syndrome or autoimmune encephalitis,

missing relevant autoantibodies can hinder differentiation from other causes of neuropathy or encephalitis (93). Identifying VGKC, CASPR2, and LGI1 antibodies is crucial for accurate diagnosis and treatment (94).

Autonomic testing is essential for diagnosing POTS and dysautonomia, which often coexist with autoimmune and ion channelopathies (95). However, it lacks the specificity to identify the underlying molecular causes. While it detects symptoms such as tachycardia and orthostatic hypotension, it does not distinguish whether they stem from autoimmune-mediated ion channel dysfunction or genetic mutations (96). This lack of specificity can lead to misdiagnosis, particularly in POTS, where symptoms overlap with conditions like hyperadrenergic states or idiopathic dysautonomia (97). Autonomic tests like heart rate variability (HRV) and tilt-table tests assess dysfunction but do not reveal immunological or genetic causes (98). In autoimmune POTS, autoantibodies such as anti-adrenergic receptor antibodies may go undetected, limiting understanding and treatment (99).

3.4 Ion Channel Function Testing

Voltage-clamp electrophysiology is a current definitive for assessing ion channel function, enabling precise measurement of ionic currents and channel conductance under controlled voltage conditions. This technique shows insights into ion channel behavior and neuronal excitability for diagnosing ion channelopathies (100). Genetic sequencing, including whole exome or specific ion channel gene panels, identifies pathogenic mutations, confirming genetic predispositions and underlying channel dysfunctions (101). Neuroimmune biomarker profiling detects inflammatory or autoimmune markers, including autoantibodies targeting ion channels, distinguishing autoimmune causes from genetic mutations and providing crucial diagnostic clarity (102). This comprehensive diagnostic approach enables precise differentiation between inflammatory conditions and hereditary channelopathies, guiding targeted therapeutic strategies.

The limitations of current testing that are known and available to clinicians underscore the need for a more integrated diagnostic approach that combines clinical evaluation with advanced molecular and serological techniques (85). Employing a comprehensive diagnostic toolkit, including genetic testing, expanded autoantibody panels, and more sensitive skin biopsy techniques—would improve the detection of rare or less understood causes of SFN, ion channelopathies, and autonomic disorders. Integrating high-throughput techniques like next-generation sequencing or proteomics may help identify new biomarkers and genetic variants associated with these conditions, improving diagnostic accuracy and enabling personalized treatments (85).

4. Long COVID and Vaccine Effects: Molecular Mechanisms and Outcomes

4.1 Long COVID Mechanisms

Persistent viral reservoirs and immune dysregulation underpin the pathophysiology of Long COVID (103). One of the key drivers of disease progression is the cGAS-STING pathway (104), activated by viral DNA, or cellular damage caused by leakage of nuclear DNA and mitochondrial DNA into the cell’s cytoplasm (105). Upon recognition of foreign or self-DNA,

cGAS binds to cytoplasmic DNA and catalyzes the production of cGAMP, which activates STING. The IFN response is triggered, inducing pro-inflammatory cytokines like IL-6, TNF-α, and IFN-γ, which perpetuate chronic inflammation and immune activation (105). The sustained inflammatory environment fuels autoimmune responses, including epitope-spreading, where viral peptides mimic self-antigens, generating autoantibodies that target neuronal and endothelial cell structures, contributing to neurological deficits and autonomic dysfunction (106).

Ion channel dysfunction plays a critical role in SFN and dysautonomia observed in Long COVID. Ion channels, like voltage-gated sodium channels (NaV1.7), are involved in nociceptive signaling and neurovascular regulation (107-109).

Chronic immune activation enhances macrophage polarization toward the M1 phenotype, releasing ROS, amplifying channelopathies and altering neural excitability. These alterations result in hyperexcitability of sensory neurons, contributing to pain syndromes, muscle weakness, and autonomic instability (110). Autoantibodies directed against ion channels like NaV1.7, VGKC, and VGCCs exacerbate these symptoms. The binding of autoantibodies to these channels disrupts their normal function, generating abnormal ion flux, further promoting hyperexcitability, neuropathic pain, and muscle weakness (111).

The symptoms linked to these autoantibodies include neuropathy, pain syndromes, muscle dysfunction, and autonomic dysfunction like orthostatic intolerance, dizziness, and tachycardia. These symptoms mirror those of conditions like small fiber neuropathy and dysautonomia, often seen in patients with Long COVID, further complicating the diagnostic process (112).

Sex-based differences are significant; females, due to X-linked immune genes and estrogen modulation, have stronger immune responses, predisposing them to more severe immune overactivation and autoantibody production (113).

4.2. Immune-Mediated Responses to Vaccination

The World Health Organization and numerous public health agencies affirm that vaccines are safe and effective, with extensive clinical trials and post-marketing surveillance demonstrating their role in preventing infectious diseases while maintaining a favorable risk-benefit profile (114).

Both mRNA-based and attenuated virus vaccines work by activating complex immune pathways, which sometimes can lead to rare, immune-mediated responses in genetically susceptible individuals (115,116). These vaccines trigger pattern recognition receptors (PRRs), like Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs), which recognize viral components and initiate immune cascades (117).

In mRNA vaccines, lipid nanoparticles (LNPs) deliver synthetic mRNA into host cells, directing spike protein synthesis and antigen presentation to T cells (118). This results in T-cell activation and antibody production.

Ion channel dysfunction, particularly in NaV, K+, or Ca2+ channels, can impair neuronal signaling and disrupt motor control, potentially leading to ataxia. The cerebellum, responsible for coordinating voluntary movement and balance, can be affected when these channels malfunction, causing uncoordinated, jerky movements. Seizure-like activity can occur due to neuronal hyperexcitability, even in the absence of epilepsy. Dysfunction in SCN1A (NaV1.1) and related ion channels has been associated with episodic convulsions, muscle rigidity, and syncope, resembling seizure disorders but with distinct underlying pathology (120).

Macrophage activation and reactive oxygen species (ROS) production have been associated with neuroinflammation and dysautonomia in certain immune-mediated conditions. The symptoms associated with autoantibody-mediated pathology include neuropathic pain, muscle weakness, tachycardia, orthostatic intolerance, and dizziness (121), closely resembling conditions like postural orthostatic tachycardia syndrome (POTS) and small fiber neuropathy (SFN) (122).

In attenuated virus vaccines, live viral components stimulate innate immune responses via PRRs, recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (123). This activation of the cGAS-STING pathway results in pro-inflammatory cytokine release, which has been implicated in autoimmune responses through molecular mimicry. As with mRNA vaccines, rare immune responses can inadvertently target self-antigens, including ion channels, potentially contributing to autoimmune neuropathy and dysautonomia (124-126).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been implicated in the dysregulation of epithelial sodium channels (ENaCs), potentially contributing to pulmonary pathology and electrolyte imbalances in COVID-19. The virus's spike protein contains a furin cleavage site identical to that of ENaC, suggesting competition for cleavage by plasmin, which may impair sodium channel function and fluid homeostasis in the lungs (127). This mechanism may also play a role in systemic dysregulation observed in Long COVID, where persistent viral antigens, immune activation, and molecular mimicry contribute to autoantibody production (128).

Emerging evidence suggests that SARS-CoV-2 may trigger autoantibody responses against ion channels, including voltage-gated sodium channels (NaV), with potential implications for neuropathic symptoms like small fiber neuropathy and autonomic dysfunction. Dysregulated immune responses, particularly excessive type I interferon (IFN-I) activation, can impair regulatory T-cell function, which may lead to the loss of immune tolerance and increased autoantibody production targeting neuronal sodium channels (129). This mechanism may underlie the overlap in clinical manifestations between Long COVID and post-vaccination immune responses, including fatigue, dysautonomia, and neuropathic pain, though their underlying pathophysiology differs. Long COVID is driven by persistent immune activation via the cGAS-STING pathway, whereas vaccine-induced responses involve transient pattern recognition receptor (PRR) activation, which in rare cases may trigger autoimmunity against ion channels (130).

Sex-based differences again play a crucial role, with females exhibiting stronger inflammatory responses due to estrogen-driven modulation of immune cells and X-linked genetic predispositions. This increased immune responsiveness may contribute to immune-mediated dysautonomia and neuropathy in predisposed individuals (131).

6. Ion Channel Modulators in the Treatment of Dysregulation Symptoms

Carbamazepine is a first choice that inhibits voltage-gated sodium channels, stabilizing neuronal membranes to prevent excessive neuronal firing. It is commonly used to manage epilepsy, trigeminal neuralgia, and neuropathic pain by reducing symptoms of muscle weakness, dysautonomia, burning pain, and tremors due to ion channel dysfunction (132).

Phenytoin also targets sodium channels, preventing repetitive neuronal firing and controlling seizures. It is used for epilepsy and neuropathic pain, helping to alleviate hyperexcitability, spasticity, and related symptoms by stabilizing ion flow within the nervous system (133).

Mexiletine is a sodium channel blocker like lidocaine, effective in treating chronic neuropathic pain and arrhythmias. By inhibiting sodium influx, it stabilizes neuronal activity, reducing pain, spasticity, and symptoms of hyperexcitability seen in conditions with ion channelopathies (134).

7. Future Therapeutic Directions

Emerging therapies for ion channelopathies include monoclonal antibodies targeting autoantibodies involved in autoimmune ion channel dysfunction, offering a promising approach for conditions like autoimmune dysautonomia and neuropathic pain (135). Future advancements, combined with personalized medicine, could provide more targeted and effective treatments for both genetic and autoimmune-driven ion channel disorders.

Discussion

Ion channel dysfunction plays a crucial role in a range of neurological and autoimmune disorders, leading to misdiagnosis due to symptom overlap with conditions like SFN, AIDP, POTS, and FND (59). This review proposes a model in which ion channelopathies, and autoimmunity converge through the activation of the cGAS-STING pathway (104). Upon exposure to foreign genetic material, including viral RNA/DNA from infections or vaccines, cGAS activation leads to STING signaling, type I interferon production, and macrophage polarization, which in turn can in rare cases, disrupt ion channel function, exacerbating autonomic and neuromuscular symptoms (23).

Ion channel dysfunction often manifests as a broad spectrum of symptoms, including POTS-like features, neuropathic pain, dysautonomia, and sensory disturbances. These symptoms closely resemble those observed in SFN, AIDP, and FND, creating diagnostic challenges (8). Although channelopathies and SFN differ mechanistically, their clinical overlap complicates differentiation and contributes to frequent misdiagnoses. Ion channel dysfunction disrupts neuronal excitability and immune regulation, producing overlapping symptoms but with distinct underlying causes,

making it crucial to consider ion channel involvement in autoimmune and inflammatory conditions.

The influence of immune responses, particularly in the context of viral infections like Long COVID and rare instances of post-vaccine inflammation, can exacerbate ion channel dysfunction (127). Immune activation, driven by STING-mediated signaling and macrophage polarization (34), promotes inflammation that affects ion channel regulation and neuronal function. Sex-based differences and ethnic variations in immune responses further complicate this landscape (4,5,113). Women exhibit heightened susceptibility to immune-mediated ion channelopathies due to hormonal modulation and X-linked genetic predispositions. Ethnic variations in STING activity may explain differences in disease prevalence and severity across populations.

Given these complexities, ion channelopathies are an underexplored yet important factor in autoimmune and chronic inflammatory diseases. Future research should focus on the molecular mechanisms linking cGAS-STING signaling, ion channel regulation, and immune activation. Additionally, exploring the gut-brain axis and the role of sex and ethnic differences in immune responses could provide crucial insights into pathogenesis and treatment strategies.

Conclusion

Ion channel dysfunction and autoimmune responses, particularly through the cGAS-STING pathway, intersect in complex ways that challenge current diagnostic and therapeutic approaches. The overlap of symptoms between ion channelopathies, SFN, AIDP, and FND underscores the need for improved diagnostic criteria that can accurately differentiate these conditions. Misdiagnosis remains a significant challenge, hindering timely intervention and appropriate treatment.

Therapeutically, targeting ion channel dysfunction and modulating the cGAS-STING pathway offers promising avenues for treating autoimmune diseases and chronic inflammation. New therapies, including STING inhibitors, ion channel blockers, and immune-modulating agents, are emerging as potential treatments. Personalized medicine, utilizing genetic profiling and immune system characterization, is critical for tailoring interventions to individuals, especially those with genetic predispositions or immune imbalances.

Future research should prioritize unraveling the intricate relationships between immune signaling, ion channel regulation, and neuroimmune interactions. Understanding the impact of sex-based immune differences and ethnic genetic variations on disease susceptibility and treatment response will be key to advancing therapeutic strategies. These findings highlight the need for a holistic approach that integrates immune regulation, ion channel function, and inflammatory processes, with broad implications for vaccine safety, autoimmune disease treatment, and the development of targeted immunotherapies.

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Conflict of Interest

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