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Mini Review

Interplay Between Sodium Homeostasis, Osmolality and Antibiotic Resistance: A Focus on Pain Transmission and SCN9A

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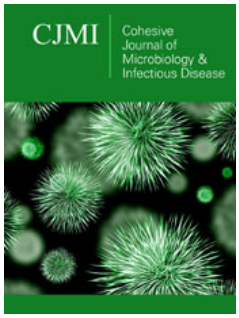

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Abstract

The SCN9A gene encodes the voltage-gated sodium channel Nav1.7, a key determinant of nociceptive signal initiation and pain perception. Pathogenic variants in SCN9A cause either extreme pain syndromes or congenital insensitivity to pain, underscoring the central role of sodium channel biology in pain physiology. Infection-related pain represents a major clinical burden and is often prolonged or exacerbated by antibiotic resistance. Beyond neuronal signaling, sodium ions and osmotic balance exert important effects on immune function, bacterial physiology and antimicrobial activity. This hypothesis paper proposes that sodium homeostasis constitutes a shared biological axis linking pain perception, host defense and bacterial adaptability. We further hypothesize that combining physiological saline with the metal chelator Ethylene Diamine Tetra Acetic Acid (EDTA) and conventional antibiotics may attenuate bacterial resistance by disrupting osmoregulatory and ion-dependent defense mechanisms, thereby indirectly improving infection-associated pain outcomes. This framework integrates neurogenetics with microbial physiology and outlines experimentally testable predictions.

Keywords: SCN9A; Nav1.7; Pain signaling; Sodium homeostasis; Osmolality; Antibiotic resistance; EDTA

Introduction

Pain and infection are deeply interconnected biological phenomena. Pain serves as an early warning signal of tissue injury and microbial invasion, while effective immune responses and antimicrobial therapy are essential for pain resolution. Failure to eradicate infection-most notably due to antibiotic resistance-often results in persistent inflammation and chronic pain states. The SCN9A gene, encoding the Nav1.7 sodium channel, is indispensable for human pain perception. Loss-of-function mutations cause congenital insensitivity to pain, whereas gain-of-function variants underlie severe pain syndromes such as inherited erythromelalgia. Although SCN9A does not directly influence microbial survival, its biology highlights the central importance of sodium fluxes in shaping pain experiences during infection. This observation motivates a broader consideration of sodium as a systemic regulator operating across neuronal, immune, and microbial domains. This paper advances the hypothesis that sodium homeostasis represents a unifying, though indirect, axis linking pain biology and antibiotic resistance and that therapeutic manipulation of ionic and osmotic environments may enhance antimicrobial efficacy [1-5].

Repositioning SCN9A: From mechanism to clinical anchor

Nav1.7 channels are highly expressed in peripheral nociceptors, where they amplify subthreshold depolarization and determine whether painful stimuli reach the threshold for action potential firing. In infectious diseases, inflammatory mediators, tissue acidosis and

immune cell activation sensitize nociceptors, often through sodium channel-dependent mechanisms [6-10].

Importantly, SCN9A is not proposed here as a molecular driver of antibiotic resistance. Rather, it serves as a clinical and conceptual anchor that underscores two key points:

A. Sodium flux is fundamental to pain generation and modulation.

B. Infection-associated pain severity and duration are clinically meaningful outcomes of antimicrobial success or failure.

Thus, SCN9A provides the neurobiological context in which persistent infection-frequently caused by resistant organisms-translates into prolonged or exaggerated pain. In this framework, reducing bacterial persistence through improved antimicrobial strategies indirectly improves pain outcomes, even without direct modulation of Nav1.7.

Sodium homeostasis beyond neurons: Immune and microbial dimensions

Sodium is the principal extracellular cation and a major determinant of serum osmolality. Disturbances such as hyponatremia and hypernatremia are common in hospitalized and critically ill patients, particularly those receiving antimicrobial therapy. Experimental and clinical evidence indicates that sodium imbalance can impair immune cell function, alter inflammatory responses and modify host susceptibility to infection.

From the microbial perspective, bacteria are highly sensitive to osmotic stress. Pathogens such as Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Klebsiella pneumoniae possess sophisticated osmoregulatory systems that enable survival across fluctuating ionic environments. These adaptations include modulation of membrane permeability, regulation of porins and efflux pumps and synthesis of Osmo protectants such as glycine betaine and proline. Crucially, many of these adaptive responses overlap with mechanisms that reduce antibiotic penetration or enhance tolerance, thereby contributing to antimicrobial resistance [11-15].

Osmolality, antibiotic activity and resistance

Changes in extracellular sodium concentration and osmolality can influence:

a) Bacterial cell wall and outer membrane permeability

b) Expression of stress-response and resistance-associated genes

c) Antibiotic diffusion, solubility and local tissue pharmacokinetics

While serum sodium does not directly equate to ionic conditions at infection sites, local microenvironments-such as abscesses, wounds or dehydrated tissues-may experience significant osmotic variation. These conditions can favor bacterial persistence and reduce antibiotic efficacy. Antibiotics themselves may exacerbate electrolyte disturbances, creating a feedback loop in which altered host ionic states and bacterial stress responses jointly promote treatment failure [16-21].

EDTA as an ionic and osmotic adjuvant

Ethylene Diamine Tetra Acetic Acid (EDTA) is a well-characterized chelator of divalent cations such as Ca^{2+} and Mg^{2+}. By destabilizing lipopolysaccharide cross-linking in Gram-negative bacteria and disrupting biofilm matrices, EDTA increases membrane permeability and enhances antibiotic penetration. I propose that EDTA's antimicrobial adjuvant effect may be potentiated in a controlled sodium environment. Physiological saline (~0.9% NaCl) provides a stable osmotic baseline, while EDTA imposes ion-dependent stress on bacterial membranes. Together, these forces may overwhelm bacterial adaptive capacity, particularly when combined with conventional antibiotics.

Central Hypothesis

I hypothesize that; The combination of physiological saline (~0.9% NaCl), low-to-moderate concentrations of EDTA and conventional antibiotics can attenuate bacterial resistance by disrupting osmoregulatory and ion-dependent defense mechanisms, thereby enhancing antimicrobial efficacy and indirectly reducing infection-associated pain. This hypothesis does not posit a direct molecular role for SCN9A in resistance, but rather situates pain biology as a clinically relevant outcome of improved infection control within a sodium-centered physiological framework.

Testable Predictions and Experimental Approaches

This hypothesis can be evaluated through:

A. In vitro susceptibility assays under controlled osmolar conditions

B. Biofilm disruption studies using EDTA-antibiotic combinations

C. Gene expression analyses of bacterial osmotic stress and resistance pathways

D. In vivo infection models assessing bacterial clearance, inflammation and pain-related behaviors

Host safety, ion balance and tissue toxicity must be rigorously assessed to ensure translational relevance.

Conclusion

SCN9A highlights the fundamental role of sodium flux in pain perception, while bacterial osmoregulation underscores sodium's importance in microbial survival and resistance. By reframing sodium homeostasis as a shared physiological backdrop rather than a single mechanistic pathway, this hypothesis integrates neurobiology, immunology and microbiology. Targeting bacterial adaptability to ionic and osmotic stress-through rational combinations of saline, EDTA and antibiotics-may represent a complementary strategy to address antibiotic resistance and its

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painful clinical consequences. Rigorous experimental validation is warranted.

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