



Brain Allergy: Molecular Mechanisms with Neuro-Immune Interactions in Light of Therapeutic Innovation

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ABSTRACT: The present review study aims to systematically analyze current knowledge on neuro-immune mechanisms across allergic diseases, evaluate emerging therapeutic strategies targeting these pathways (including neuropeptide antagonists and TRP channel modulators), and identify critical gaps for future research to enable development of novel, dual-targeting treatments that address both neural and immunological components of allergy pathogenesis. Allergic diseases such as asthma, atopic dermatitis, and allergic rhinitis are increasingly understood as disorders of dysregulated neuro-immune crosstalk, where bidirectional interactions between sensory neurons and immune cells amplify inflammation through neuropeptides (substance P, CGRP), neurotrophies (NGF, BDNF), and autonomic signaling. The bidirectional relationship between stress pathways and allergic inflammation involves complex neuroendocrine-immune interactions. The behavioural and cognitive aspects of allergy demonstrate the profound integration between psychological processes and immune function. The remarkable capacity of the nervous system to modulate immune responses through learned associations is exemplified by classical conditioning experiments in allergic disorders. This review study synthesizes mechanisms like mast cell-neuron feedback loops, stress-induced glucocorticoid resistance, and disease-specific pathways (e.g., IL-31/TRPV1+ in itch, vagal-plasma cell circuits in asthma), while highlighting behavioural influences (Pavlovian conditioning, stress) and emerging therapies targeting neuro-immune axes (NK1R antagonists, TRP modulators). Therapeutically, novel approaches targeting neuro-immune interfaces show promise, including NK1 receptor antagonists, TRP channel modulators, and neurotrophic inhibitors, though challenges remain in achieving tissue specificity and preserving physiological neural functions. This knowledge opens new therapeutic possibilities that extend beyond conventional immunosuppression. Challenges in developing tissue-specific interventions and the need for integrated, biomarker-driven approaches are discussed, offering a roadmap for next-generation allergy treatments that address both neural and immunological dysfunction.

Keywords: Neuro-immune axis, Allergic inflammation, Neuropeptides, Precision therapy.

INTRODUCTION

Allergic diseases, including allergic rhinitis (AR), asthma, atopic dermatitis (AD), food allergies, and chronic urticaria (CU), represent a significant global health burden characterized by dysregulated type 2 (T2) immune responses involving IgE-mediated mast cell activation, eosinophil infiltration, and pro-inflammatory cytokine release (Chen et al., 2024a). Emerging evidence highlights the critical role of bidirectional neuro-immune interactions in modulating allergic inflammation, where sensory neurons release neuropeptides like substance P (SP) and calcitonin gene-related peptide (CGRP) that induce vasodilation and immune cell recruitment (Voisin et al., 2017), while mast cells located near nerve fibres express receptors for these neuropeptides (NK1R, MRGPRX2), creating a feedback loop that amplifies inflammation (Toyoshima and Okayama, 2022). In AD, this interplay manifests as the pruritogenic "itch-scratch cycle," where mast cell-derived histamine and tryptase activate sensory neurons (Szöllösi et al., 2022), and neurotrophies like nerve growth factor (NGF) promote neuronal sensitization and hyperinnervation (Lio and McCarthy, 2025). The respiratory tract demonstrates similar mechanisms, with neuropeptides from vagal and dorsal root ganglion neurons exacerbating airway hyperresponsiveness in asthma (Chen et al., 2024b), while psychological factors like stress modulate disease severity through glucocorticoid release and conditioned immune responses (Pivac et al., 2023). This review aims to systematically analyze current knowledge on neuro-immune mechanisms across allergic diseases, evaluate emerging therapeutic strategies targeting these pathways (including neuropeptide antagonists and TRP channel modulators), and identify critical gaps for future research to enable development of novel, dual-targeting treatments that address both neural and immunological components of allergy pathogenesis.

Neuro-Immune Interactions: Mechanisms and Pathways

The intricate crosstalk between the nervous and immune systems forms a critical axis in the pathophysiology of allergic diseases, mediated through complex cellular and molecular mechanisms involving both the peripheral (PNS) and central nervous systems (CNS) (Boahen et al., 2023). The PNS, comprising sensory, sympathetic, and parasympathetic neurons, densely innervates barrier tissues such as the skin, respiratory tract, and gastrointestinal mucosa, where it interacts directly with immune cells to modulate inflammatory responses (Duan et al., 2021). Sensory neurons detect allergens and inflammatory mediators through specialized receptors, transmitting signals to the CNS while simultaneously releasing neuropeptides that act locally on immune cells. The CNS, in turn, processes these signals and modulates immune activity through autonomic and neuroendocrine pathways, creating a bidirectional communication network that significantly influences allergic disease progression (Han et al., 2025).

Key neurotransmitters and neuropeptides serve as crucial mediators of neuro-immune interactions in allergic inflammation. Substance P (SP), released primarily by sensory neurons, binds to neurokinin-1 receptors (NK1R) on mast cells, triggering degranulation and the release of histamine, leukotrienes, and cytokines that amplify inflammation (Ruppenstein et al., 2025). Calcitonin gene-related peptide (CGRP), another sensory neuropeptide, induces vasodilation and plasma extravasation while modulating dendritic cell function to promote Th2 polarization. Vasoactive intestinal peptide (VIP), produced by parasympathetic neurons, exhibits dual roles - it can suppress inflammation through inhibition of macrophage activation but also promotes type 2 immunity by stimulating IL-5 and IL-13 production from innate lymphoid cells (ILC2s). These neuropeptides create a complex regulatory network where their effects depend on tissue context, receptor expression patterns, and disease stage (Russo and Hay, 2023).

Neurotrophies, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), represent another critical class of mediators in neuro-immune crosstalk¹³. Produced by both neurons and immune cells, NGF promotes neuronal survival and sensitization while simultaneously activating mast cells and eosinophils, creating a positive feedback loop that sustains inflammation (Voisin et al., 2017). In allergic rhinitis and asthma, elevated NGF levels correlate with disease severity and contribute to neuronal hyper reactivity and tissue remodelling (Konstantinou et al., 2022). BDNF, primarily derived from eosinophils and epithelial cells, enhances neuronal excitability and promotes the release of additional pro-inflammatory mediators, further amplifying neurogenic inflammation (Voisin et al., 2017). These neurotrophies also influence immune cell trafficking and survival, with NGF inhibiting eosinophil apoptosis and BDNF modulating T cell responses (Konstantinou et al., 2022).

The bidirectional communication between neurons and immune cells involves multiple cellular players that express receptors for neural mediators. Mast cells, strategically located near nerve endings, express receptors for SP (NK1R and MRGPRX2), CGRP (CLR/RAMP1), and neurotransmitters including acetylcholine and norepinephrine (Gentile et al., 2021). This allows them to respond rapidly to neuronal signals while simultaneously releasing mediators that activate sensory neurons, creating a self-perpetuating cycle of inflammation. Eosinophils, key effector cells in allergic inflammation, express receptors for neuropeptides and neurotrophies, through which they contribute to neuronal sensitization and tissue remodeling (Klimov et al., 2022). T cells and dendritic cells complete this neuro-immune circuit by responding to VIP and other neuropeptides that modulate their activation, cytokine production, and migratory behaviour. Dendritic cells in particular form close associations with nerve fibres in inflamed tissues, where they integrate neural and immunological signals to shape adaptive immune responses (Shouman and Benarroch, 2022).

This complex interplay between neural and immune components creates multiple potential therapeutic targets for allergic diseases. Interventions could aim to block specific neuropeptide receptors, modulate neurotrophic signalling, or disrupt pathological neuro-immune synapses (Krsek et al., 2024). However, the pleiotropic effects of these mediators and their tissue-specific roles present significant challenges for therapeutic development, necessitating a deeper understanding of the precise mechanisms governing neuro-immune interactions in different allergic conditions (Bulgur et al., 2024). Future research should focus on elucidating these context-dependent effects and developing strategies to selectively target pathological neuro-immune signalling while preserving beneficial homeostatic functions.

Neuro-Immune Interactions in Specific Allergic Diseases

Allergic rhinitis (AR)

The nasal mucosa represents a prime example of neuro-immune crosstalk, where neural hyperresponsiveness contributes significantly to symptom generation (Klimov et al., 2022). In AR, allergen exposure triggers mast cell degranulation and subsequent release of inflammatory mediators that activate trigeminal sensory neurons, leading to characteristic symptoms of sneezing, rhinorrhoea, and nasal congestion (Zhou et al., 2023). The neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP) play pivotal roles, with SP inducing mast cell degranulation and plasma extravasation through NK1 receptors, while CGRP mediates vasodilation and glandular secretion (Singh et al., 2022). Neurotrophies, particularly nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), are markedly elevated in AR patients and contribute to neuronal sensitization and eosinophil activation (Liu et al., 2023). The autonomic nervous system further modulates nasal inflammation,

where parasympathetic activation via acetylcholine and vasoactive intestinal peptide (VIP) promotes glandular secretion, while sympathetic input through norepinephrine induces vasoconstriction (Czerwaty et al., 2022).

Chronic rhinosinusitis (CRS)

In CRS, particularly the nasal polyp variant (CRSwNP), neurogenic inflammation contributes to polyp formation and disease chronicity (Czerwaty et al., 2022). The sinus mucosa demonstrates increased expression of NGF and hemokinin-1, with eosinophilic polyps showing particularly high levels of neurokinin 1 receptor (NK1R) expression (Zhou et al., 2023). Tachykinins, including SP and neurokinin A, promote fibrin deposition and edema through their effects on vascular permeability and glandular secretion (Al Mamun et al., 2025). Interestingly, CRS patients show altered neurotrophic profiles compared to controls, with elevated NGF but decreased BDNF levels, suggesting distinct neuroimmune mechanisms in polyp formation versus non-polypoid CRS (Nicoletti et al., 2022). These neuroimmune interactions contribute to the characteristic tissue remodelling observed in CRS, including basement membrane thickening and glandular hyperplasia (Czerwaty et al., 2022).

Allergic asthma

The airways demonstrate complex neuroimmune regulation, where sensory neurons contribute significantly to airway hyperresponsiveness (AHR). Vagal sensory neurons release SP and CGRP upon activation by inflammatory mediators, promoting bronchoconstriction and mucus hypersecretion (Trevizan-Bau and Mazzone, 2023). A unique feedforward loop exists between IgE-producing plasma cells, FcεRI-expressing vagal sensory neurons, and Th2 cells that amplifies allergic airway inflammation. Psychological factors markedly influence asthma severity, with stress increasing airway inflammation through β2-adrenergic receptor desensitization and glucocorticoid resistance. Notably, Pavlovian conditioning experiments demonstrate that asthma symptoms can be elicited by neutral stimuli previously paired with allergens, highlighting the CNS role in disease modulation (Plum et al., 2024).

Food Allergy

The enteric nervous system (ENS) plays a crucial role in food allergy manifestations, coordinating protective responses like vomiting and diarrhea. Mast cells in the intestinal submucosa form close associations with enteric neurons, where they communicate via histamine, prostaglandins, and leukotrienes (Salvo-Romero et al., 2022). In food protein-induced enterocolitis syndrome (FPIES), this neuroimmune interaction mediates rapid emesis through activation of the chemoreceptor trigger zone. Behavioural conditioning significantly influences food allergy responses, with animal studies demonstrating that taste aversion can be conditioned to allergen exposure (Matatia et al., 2024). Furthermore, repeated allergen consumption in sensitized mice induces depression-like behaviour without overt allergic reactions, suggesting CNS effects of peripheral food allergy (Smith, 2021).

Atopic dermatitis (AD)

AD pathogenesis involves intricate neuroimmune circuits that drive chronic pruritus. The cytokine IL-31, produced by Th2 cells, directly activates TRPV1⁺ sensory neurons to induce itch, while simultaneously promoting nerve fibre elongation (Ständer et al., 2024). IL-4 and IL-13 enhance neuronal sensitivity to multiple pruritogens by increasing TRPV1 expression in sensory neurons. Keratinocyte-derived thymic stromal lymphopoietin (TSLP) activates a distinct subset of sensory neurons through TRPA1 channels, creating an epithelial-neuronal itch axis (Konstantinou et al., 2022). The close anatomical association between mast cells and nerve fibres in AD skin facilitates bidirectional communication, where mast cell proteases activate neuronal PAR2 receptors while SP released from neurons triggers mast cell degranulation via MRGPRX2 (Zhou et al., 2023).

Chronic urticaria (CU)

In CU, mast cell-nerve interactions drive wheal formation through neuropeptide-mediated vasodilation. SP levels correlate with disease severity and can induce wheal-and-flare reactions through both NK1 receptors and MRGPRX2 on mast cells (Bhuiyan et al., 2021). The cutaneous HPA axis becomes dysregulated in CU, with increased expression of corticotropin-releasing hormone (CRH) receptors on mast cells. Stress exacerbates CU through multiple mechanisms, including disruption of cortisol circadian rhythms and CRH-induced mast cell degranulation. Psychological comorbidities are prevalent in CU patients, with approximately 30% exhibiting anxiety or depression, further highlighting the brain-skin connection in this condition (Yang et al., 2025).

Behavioural and Cognitive Aspects of Neuro-Immune Interactions

Pavlovian conditioning in allergic diseases

The remarkable capacity of the nervous system to modulate immune responses through learned associations is exemplified by classical conditioning experiments in allergic disorders (Kennedy and Silver, 2022). In ground breaking studies, guinea pigs sensitized to bovine serum albumin developed elevated histamine levels when re-exposed solely to the paired odour stimulus (dimethyl sulphide), demonstrating immune memory formation independent of allergen exposure. Human studies reveal similar phenomena, where allergic rhinitis patients exhibited conditioned nasal tryptase release when presented with gustatory stimuli previously associated with allergen challenges (Backaert et al., 2022). The neural circuitry underlying these conditioned responses likely involves limbic system projections to brainstem nuclei that regulate autonomic outflow to immune tissues (Koban et al., 2021). Importantly, conditioned immunosuppression has therapeutic potential, as demonstrated by studies where placebo treatments paired with desloratadine achieved comparable reductions in skin prick test reactivity and basophil activation to active drug treatment (Sondermann et al., 2021). (Klimov, 2021).

Stress and allergic inflammation

The bidirectional relationship between stress pathways and allergic inflammation involves complex neuroendocrine-immune interactions (Klimov, 2021). Chronic stress exposure in urban environments correlates with asthma prevalence, with neighbourhood violent crime rates showing significant associations with childhood asthma diagnosis rates independent of other confounders (Han et al., 2023). Molecular studies reveal that stress-induced cortisol release paradoxically enhances airway inflammation in murine models, while simultaneously reducing responsiveness to corticosteroids. Genetic polymorphisms in stress-related genes (e.g., ADCYAP1R1) interact with chronic stress to influence bronchodilator response in asthma patients. In atopic dermatitis, stress-induced neuropeptide release (particularly substance P) activates mast cells through both NK1 and MRGPRX2 receptors, amplifying itch-scratch cycles and skin barrier disruption (Steinhoff et al., 2022).

Psychoneuroimmunology of allergy

Translational research bridges animal models and human studies to elucidate mind-body connections in allergy (Warren et al., 2025). Murine contact dermatitis models demonstrate that cyclosporin effects can be behaviourally conditioned through saccharin pairing, with re-exposure to saccharin alone suppressing contact hypersensitivity responses (Andreone et al., 2023). Human psychoneuroimmunology studies reveal that examination stress in asthmatic students potentiates IL-5 production and eosinophil mobilization following bronchial challenge. The emerging field of epigenetics provides mechanisms for these effects, with stress-associated DNA methylation patterns identified in genes related to asthma pathogenesis. Notably, allergic inflammation itself can influence CNS function, as demonstrated by food allergy models where repeated allergen consumption induces depression-like behaviours and altered brain histamine receptor expression without peripheral symptoms (Germundson and Nagamoto-Combs, 2022).

CONCLUSION

The emerging understanding of neuro-immune interactions in allergic diseases reveals a sophisticated biological dialogue that transcends traditional immunological paradigms. The nervous system does not merely respond to allergic inflammation but actively shapes immune responses through multiple pathways - from neuropeptide signalling and neurotrophic-mediated crosstalk to conditioned immune modulation and stress-induced neuroendocrine changes. These interactions occur across all allergic conditions, though with tissue-specific variations that account for the diverse clinical manifestations observed in asthma, atopic dermatitis, food allergies, and other allergic disorders. The behavioural and cognitive aspects of allergy demonstrate the profound integration between psychological processes and immune function. Pavlovian conditioning experiments prove that allergic responses can be learned and modified through experience, while chronic stress studies reveal how environmental factors can become biologically embedded to worsen disease outcomes. These findings fundamentally change our conceptualization of allergies from simple hypersensitivity reactions to complex neuro-immune disorders influenced by both internal physiology and external experiences. This knowledge opens new therapeutic possibilities that extend beyond conventional immunosuppression. Potential interventions could target neural signaling pathways, modulate stress responses, or harness the power of conditioned immune regulation. However, significant challenges remain in translating these concepts into clinical practice, particularly in developing precise interventions that account for individual neuro-immune profiles without disrupting essential homeostatic functions. Future research should focus on elucidating the specific neural circuits involved in allergic inflammation, identifying biomarkers of neuro-immune dysregulation, and developing integrated treatment approaches that address both the immunological and neurological components of disease. As our understanding of these mechanisms grows, we move closer to a new era of allergy management that considers the whole patient - their immune system, nervous system, and lived experiences - in developing personalized, effective treatments.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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