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NEURO-ENDOCRINE-IMMUNE CROSSTALK IN CHRONIC DISEASES: AN INTEGRATIVE REVIEW OF MOLECULAR MECHANISMS, BIOMARKERS, AND PREVENTIVE STRATEGIES

Paulina Patrycja Turzyńska *(Corresponding Author, Email: turzynska10@gmail.com)*
University Clinical Centre, Gdansk, Pomerania, Poland
ORCID ID: 0009-0000-4072-8213

Marcjanna Maria Liedtke
Cardinal Stefan Wyszynski University in Warsaw, Warsaw, Mazovia, Poland
ORCID ID: 0009-0008-6442-9312

Alicja Biskup
Uniwersyteckie Centrum Stomatologii Śląskiego Uniwersytetu Medycznego w Katowicach sp. z o.o., Bytom, Poland
ORCID ID: 0009-0001-2228-1478

Agata Wnęk
5 Wojskowy Szpital Kliniczny z Polikliniką SP ZOZ w Krakowie, Poland
ORCID ID: 0009-0004-5384-4597

Weronika Martynowska
Prof. W. Orłowski Independent Public Clinical Hospital of the Medical Centre of Postgraduate Education, Poland
ORCID ID: 0009-0003-6403-6926

Dastin Misiaszek
Medical University of Warsaw, Warsaw, Mazovia, Poland; Medical Intern, University Clinical Center of the Medical University of Warsaw
ORCID ID: 0009-0000-6932-9515

Natalia Grabowska
Specjalistyczny Szpital Wojewódzki w Ciechanowie, Ciechanów, Mazowieckie, Poland
ORCID ID: 0009-0007-9797-4416

Anna Wolszczak
Independent Public Clinical Hospital of Prof. W. Orlowski CMKP in Warsaw, Poland
ORCID ID: 0009-0006-7348-1185

ABSTRACT

Background: The growing burden of chronic non-communicable diseases has highlighted the importance of the neuro-endocrine-immune (NEI) axis as a central regulatory network integrating neural, endocrine, and immune signaling to maintain physiological homeostasis and coordinate adaptive responses to internal and environmental challenges. Increasing evidence indicates that disruption of this bidirectional communication contributes to chronic low-grade inflammation, impaired stress adaptation, and the development of multiple chronic diseases.
Objective: This integrative review aims to synthesize current evidence on the molecular mechanisms, regulatory networks, biomarkers, and translational implications of neuro-endocrine-immune crosstalk, with particular emphasis on its relevance for preventive strategies and personalized medicine.
Materials and Methods: An integrative review of peer-reviewed literature indexed in PubMed, Scopus, and Web of Science was conducted. The available evidence was synthesized to identify key molecular pathways, neuroimmune regulatory mechanisms, environmental sensing pathways, and clinically relevant biomarkers associated with neuro-endocrine-immune (NEI) dysregulation.
Results: The available evidence indicates that disruption of NEI crosstalk promotes persistent inflammatory activation, autonomic imbalance, impaired glucocorticoid signaling, and immune dysregulation, thereby contributing to the initiation and progression of major chronic diseases. Inflammatory mediators, cortisol dynamics, autonomic indices, microbiota-derived metabolites, and environmental sensing pathways have emerged as promising biomarkers and therapeutic targets for disease prevention and risk stratification.
Conclusions: The NEI axis represents a fundamental systems-level interface linking environmental exposures, stress responses, and chronic disease development. A deeper understanding of NEI crosstalk provides a scientific basis for identifying clinically relevant biomarkers and supports the development of predictive, preventive, personalized, and participatory strategies for chronic disease prevention and management.

KEYWORDS

Policy development, School Management, Indiscipline, Leadership, Challenges and Strategies

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1. Introduction

The growing global burden of chronic non-communicable diseases has shifted biomedical research from organ-centered concepts toward systems-level models that emphasize the complex interactions governing physiological homeostasis and disease development. Among the key regulatory networks emerging from this systems-based perspective, the neuro-endocrine-immune (NEI) axis is increasingly recognized as a fundamental biological framework coordinating bidirectional communication between the nervous, endocrine, and immune systems [1-6]. Through tightly coordinated signaling pathways involving cytokines, hormones, neurotransmitters, neuropeptides, and neural circuits, the NEI axis integrates environmental and endogenous stimuli to orchestrate adaptive responses while maintaining immune competence, metabolic balance, and tissue homeostasis [1,5,6]. Growing evidence further demonstrates that disruption of this integrated communication network promotes chronic low-grade inflammation, impaired stress adaptation, and immune dysregulation, thereby contributing to the development and progression of cardiovascular, metabolic, autoimmune, neurodegenerative, psychiatric, and neoplastic diseases [6,12-21]. Collectively, these findings establish NEI crosstalk as a unifying systems-level framework linking molecular mechanisms with chronic disease pathogenesis and supporting the development of integrative approaches to disease prevention and personalized medicine.

A defining feature of the neuro-endocrine-immune (NEI) axis is its ability to integrate diverse biological signals through continuous bidirectional communication among the nervous, endocrine, and immune systems.

Rather than functioning as independent regulatory entities, these systems form an interconnected network that continuously adapts to physiological and environmental challenges to preserve systemic homeostasis. This integrated signaling network is mediated by cytokines, hormones, neurotransmitters, neuropeptides, and autonomic neural circuits, enabling the rapid detection of internal and external perturbations and the coordinated regulation of immune, endocrine, and neural functions. Beyond maintaining physiological homeostasis, the NEI axis coordinates adaptive responses to infection, tissue injury, metabolic imbalance, and psychological stress by synchronizing inflammatory, neuroendocrine, and metabolic pathways [1,5,6]. One of the most significant advances in this field has been the discovery of specialized neuroimmune regulatory circuits, particularly the vagus nerve-mediated inflammatory reflex, which demonstrated that the nervous system actively modulates immune function through rapid and precisely coordinated anti-inflammatory signaling rather than merely responding to immune activation [2,3,5]. Collectively, these discoveries have reshaped the understanding of immune regulation by establishing the NEI axis as a dynamic, multilevel regulatory network in which molecular, cellular, and organ-level interactions determine the initiation, magnitude, and resolution of immune responses while preserving systemic homeostasis.

The integrity of neuro-endocrine-immune (NEI) communication is essential for maintaining physiological resilience and enabling coordinated adaptation to continuously changing internal and environmental conditions. However, persistent exposure to psychological, metabolic, environmental, and inflammatory stressors can progressively disrupt the tightly regulated interactions among the nervous, endocrine, and immune systems, reducing their capacity to maintain physiological equilibrium [12-16]. Rather than remaining confined to individual biological systems, these disturbances propagate across interconnected signaling networks, creating self-amplifying feedback loops characterized by autonomic imbalance, neuroendocrine dysfunction, immune activation, and persistent low-grade inflammation. As these maladaptive processes become sustained, they impair glucocorticoid responsiveness, disrupt cytokine signaling, compromise the resolution of inflammation, and promote progressive tissue dysfunction, thereby increasing susceptibility to chronic disease [12-21]. Accumulating evidence indicates that these interconnected mechanisms constitute a shared pathophysiological foundation underlying cardiovascular, metabolic, autoimmune, neurodegenerative, psychiatric, and neoplastic disorders despite their diverse clinical manifestations [17-21]. Collectively, these findings support the concept of NEI dysregulation as a central systems-level mechanism that links chronic stress, immune dysfunction, and persistent inflammation with the initiation, progression, and clinical heterogeneity of chronic diseases.

Despite remarkable advances in neuroimmunology, systems biology, and precision medicine, the current understanding of neuro-endocrine-immune (NEI) crosstalk remains fragmented, with important mechanistic insights dispersed across multiple scientific disciplines. Most experimental studies and review articles have focused on individual components of the NEI axis-including hypothalamic-pituitary-adrenal (HPA) axis dysfunction, neuroinflammation, chronic low-grade inflammation, aryl hydrocarbon receptor (AhR) signaling, and microbiota–gut–brain communication-whereas comparatively few have integrated these interconnected mechanisms within a unified systems-level framework [7-29]. At the same time, rapid advances in molecular biology, immunometabolism, environmental sensing, multi-omics technologies, and systems medicine have substantially expanded the understanding of NEI regulation, facilitating the identification of novel biomarkers and potential therapeutic targets with increasing translational relevance [17,22-37]. However, the growing complexity of these discoveries underscores the need for comprehensive integrative reviews that critically synthesize molecular mechanisms, biomarker signatures, and preventive strategies into a coherent conceptual framework. Addressing this knowledge gap is essential for translating systems-level discoveries into clinically actionable approaches that support early disease detection, risk stratification, targeted prevention, and personalized medicine.

2. Methodology

This study was conducted as an integrative narrative review to synthesize and critically evaluate current knowledge on neuro-endocrine-immune (NEI) crosstalk in chronic diseases. A structured literature search was performed using the PubMed, Scopus, and Web of Science databases to identify peer-reviewed publications relevant to the objectives of this review. The search strategy combined controlled vocabulary, where applicable, with free-text keywords related to neuro-endocrine-immune crosstalk, neuroimmune communication, the hypothalamic-pituitary-adrenal (HPA) axis, chronic inflammation, neuroinflammation, the microbiota-gut-brain axis, the aryl hydrocarbon receptor (AhR), biomarkers, and chronic diseases. To ensure comprehensive coverage of the topic, the reference lists of selected publications were manually screened to identify additional

relevant studies. Original research articles, systematic reviews, meta-analyses, and narrative reviews were considered for inclusion according to their scientific relevance, methodological quality, and contribution to understanding the molecular and translational aspects of NEI regulation. The collected evidence was critically appraised and synthesized using a thematic narrative approach, enabling the integration of findings on molecular signaling pathways, neuroimmune regulatory mechanisms, biomarker profiles, and preventive strategies relevant to chronic disease prevention and personalized medicine.

3. Research results

3.1. Neural and molecular mechanisms of NEI crosstalk

Neuro-endocrine-immune (NEI) communication is mediated through tightly coordinated bidirectional signaling pathways that integrate neural, endocrine, and immune responses into a unified regulatory network [1-6]. A key component of this system is the inflammatory reflex, in which vagus nerve signaling enables rapid and spatially precise modulation of cytokine production, complementing slower endocrine pathways [2,3,5].

At the molecular level, cytokines act as critical mediators linking peripheral immune activation with central nervous system responses, influencing behavior, cognition, and mood. These processes are supported by extensive evidence demonstrating the role of neuroimmune interactions in brain function and behavior [7-11].

Microglia, as resident immune cells of the central nervous system, play a central role in these processes by contributing to synaptic remodeling, neuroinflammation, and neurodegeneration [8-10]. At the cellular level, these interactions are mediated through receptor-dependent pathways-including cytokine receptors, glucocorticoid receptors, and neurotransmitter signaling systems-enabling precise integration of immune and neural responses. In addition, neurotransmitters such as acetylcholine and catecholamines directly modulate immune cell activity, further reinforcing neuroimmune integration.

Together, these mechanisms illustrate how neural and immune signaling are functionally integrated across molecular, cellular, and systems levels.

3.2. Stress and HPA axis dysregulation

Chronic stress represents a major disruptor of NEI homeostasis through alterations in hypothalamic-pituitary-adrenal (HPA) axis dynamics [12-15]. While glucocorticoids normally exert anti-inflammatory and regulatory effects, sustained activation of the HPA axis leads to glucocorticoid resistance, impaired feedback regulation, and persistent immune activation [12,14,15].

Psychosocial factors further modulate these responses. The social safety theory provides a framework linking perceived environmental threats with inflammatory signaling and increased disease risk, highlighting the integration of environmental and biological processes [16]. In parallel, chronic stress alters autonomic nervous system balance-characterized by increased sympathetic and reduced parasympathetic activity—thereby amplifying inflammatory signaling and disrupting immune regulation.

These stress-induced alterations directly contribute to the development of chronic low-grade inflammation, linking neuroendocrine dysregulation with systemic immune activation.

3.3. Chronic inflammation as a systems-level mechanism

Chronic low-grade inflammation emerges as a central consequence of NEI dysregulation and is widely recognized as a key driver of chronic disease pathogenesis across multiple systems [17-21]. In contrast to acute inflammation, which is self-limiting, chronic inflammation is characterized by persistent immune activation, impaired resolution, and progressive tissue damage [18,20].

The concept of metaflammation integrates metabolic and inflammatory processes, linking excess nutrient availability with systemic immune activation [17]. At the molecular level, this process involves sustained activation of inflammatory transcription factors, including NF-κB signaling pathways, along with alterations in immune cell metabolism and cytokine production. These processes are closely linked to immunometabolic reprogramming, in which metabolic pathways within immune cells directly shape inflammatory responses. In cardiovascular disease, inflammatory mechanisms drive atherosclerosis and represent important therapeutic targets [19,20].

3.4. Environmental and microbiota-mediated regulation

Environmental signals modulate NEI crosstalk through specialized molecular sensing pathways. The aryl hydrocarbon receptor (AhR) acts as a key integrator of environmental, dietary, and microbial signals, influencing immune cell differentiation and inflammatory responses [22-26].

The microbiota-gut-brain axis further extends NEI regulation, with microbial metabolites modulating immune and neuroendocrine signaling [27,28]. Key mediators of these interactions include short-chain fatty

acids and tryptophan-derived metabolites, which influence immune cell function, barrier integrity, and neural signaling pathways. Disruption of microbiota composition (dysbiosis) is associated with altered immune responses and increased susceptibility to chronic diseases [29].

3.5. NEI dysregulation across chronic diseases

NEI dysregulation contributes to multiple chronic diseases through shared and convergent mechanisms involving inflammation, neuroendocrine imbalance, and immune dysfunction.

In neurodegenerative and psychiatric disorders, neuroinflammation and cytokine signaling alter neuronal function and behavior [7,11]. In cardiovascular disease, neuroimmune interactions promote atherosclerosis and heart failure progression [19,20]. In kidney disease and cancer, neural and immune pathways interact to drive inflammation, tissue damage, and disease progression [30–32].

Recent integrative studies further support the concept of neuro-endocrine-immune complex modulation as a systemic regulatory mechanism. Collectively, these findings highlight the systemic nature of NEI dysregulation and its role in shaping disease-specific pathophysiological trajectories.

3.6. Biomarkers and translational implications

Integrated biomarker profiles-including inflammatory mediators, neuroendocrine hormones, autonomic indices, and microbiome-associated markers-reflect NEI dysregulation and provide clinically relevant tools for disease risk assessment and monitoring [17,21,27]. Integration of these biomarkers with multi-omics approaches may further enhance their predictive value and enable more precise characterization of disease trajectories.

Targeted modulation of NEI interactions, including stress regulation and anti-inflammatory strategies, represents a promising and translationally relevant approach for prevention and personalized medicine. Emerging evidence suggests that adaptogenic compounds modulate neuroendocrine and immune responses, enhancing stress resilience and reducing inflammation [33–35]. These effects are mediated through modulation of stress signaling pathways, inflammatory cascades, and metabolic regulation, reflecting a multi-target mode of action.

These findings further support the application of predictive, preventive, personalized, and participatory (P4) medicine approaches for early detection, risk stratification, and targeted intervention in chronic diseases [36,37].

Taken together, these results position NEI dysregulation as a central systems-level mechanism linking environmental exposures, stress responses, and chronic disease development.

4. Discussion

The present review provides an integrative synthesis of neuro-endocrine-immune (NEI) crosstalk as a central regulatory axis in the pathophysiology of chronic diseases. Interactions between the nervous, endocrine, and immune systems form a dynamic, interconnected network governing both physiological homeostasis and maladaptive responses [1-6]. Importantly, this network operates as a hierarchical and adaptive system in which local molecular events can propagate across organ systems, amplifying systemic responses and shaping disease trajectories.

A central concept emerging from this analysis is that NEI dysregulation represents a shared, system-level mechanism underlying a broad spectrum of chronic conditions, including cardiovascular, metabolic, neurodegenerative, psychiatric, and oncological disorders [7-11,17-21,30-32]. Despite their clinical heterogeneity, these conditions exhibit convergent biological features-most notably chronic low-grade inflammation, dysregulated stress responses, and immune imbalance-supporting a unified model of systemic dysfunction. This convergence suggests that disease-specific phenotypes may arise from common regulatory disturbances, modulated by genetic, environmental, and lifestyle-related factors.

A key mechanistic feature of NEI crosstalk is the presence of bidirectional and self-amplifying feedback loops linking neural signaling, endocrine regulation, and immune activation [1-6]. Chronic stress represents a central driver of this dysregulation: sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis leads to altered glucocorticoid signaling, impaired feedback regulation, and persistent inflammatory activation [12-16]. Conversely, immune-derived mediators influence central nervous system function and neuroendocrine signaling, further reinforcing maladaptive regulatory loops. These feedback mechanisms may contribute to the transition from adaptive physiological responses to stable pathological states, thereby sustaining disease chronicity.

Within this integrative model, chronic low-grade inflammation can be conceptualized as a stable systems-level state rather than a transient pathological event. The concept of metaflammation integrates

metabolic and immune pathways [17], while large-scale analyses confirm the role of chronic inflammation as a key driver of disease across the lifespan [18-21]. In cardiovascular disease, inflammatory mechanisms directly contribute to atherosclerotic progression and clinical outcomes [19,20].

Environmental and lifestyle factors further modulate NEI dynamics by shaping regulatory set points. The aryl hydrocarbon receptor (AhR) acts as a key ligand-activated molecular integrator linking environmental, dietary, and microbial signals with immune regulation [22-26]. In parallel, the microbiota-gut-brain axis represents a major interface between environmental inputs and host physiology, mediating neuroimmune communication through metabolic and neural pathways [27-29]. These findings highlight the continuous interaction between external exposures and internal regulatory systems, reinforcing the concept of the NEI axis as a dynamic interface between environment and host physiology.

The convergence of these mechanisms across multiple disease domains supports a unified model of chronic disease pathogenesis. Neuroimmune processes contribute to neurodegenerative and psychiatric disorders [7-11], while in peripheral systems they influence kidney disease, cancer progression, and other chronic conditions [30-32]. These findings further reinforce the concept that organ-specific pathologies represent context-dependent manifestations of systemic regulatory imbalance. Recent integrative studies further support the concept of neuro-endocrine-immune complex modulation as a systemic regulatory mechanism.

From a translational perspective, NEI crosstalk provides a robust foundation for clinically actionable, multi-dimensional biomarker strategies. Composite biomarker profiles integrating immune, neuroendocrine, and metabolic parameters may improve early detection, risk stratification, and monitoring of disease progression [17,21,27]. Moreover, interventions targeting regulatory networks-including stress modulation, anti-inflammatory strategies, microbiota-targeted therapies, and adaptogenic compounds-represent promising approaches for comprehensive disease management. Such multi-target approaches may offer advantages over single-pathway interventions by addressing the underlying regulatory complexity of chronic diseases [33–35].

These approaches align with the principles of systems medicine and predictive, preventive, personalized, and participatory (P4) medicine, emphasizing early intervention and individualized care strategies [36,37].

Despite these advances, significant challenges remain. The complexity of NEI interactions limits causal inference, and much of the current evidence is derived from preclinical models with limited translational applicability. In addition, inter-individual variability and heterogeneity in biomarker measurement and study design complicate the development of standardized therapeutic approaches and hinder clinical implementation.

Future research should prioritize integrative, systems-level approaches incorporating multi-omics data, longitudinal human studies, and advanced computational modeling. Such strategies will be essential for capturing the dynamic nature of NEI interactions and translating mechanistic insights into clinically actionable frameworks.

Importantly, the NEI axis may be conceptualized as a dynamic, multi-scale regulatory network characterized by nonlinear interactions and emergent properties. Within this framework, relatively small perturbations in one subsystem may propagate across interconnected pathways, leading to disproportionate system-wide effects. This systems-level perspective emphasizes the role of network resilience, adaptive capacity, and threshold-dependent transitions in determining whether physiological responses remain adaptive or shift toward stable pathological states.

Overall, these findings support a paradigm shift from reductionist models toward a systems-level understanding of chronic disease pathogenesis. Neuro-endocrine-immune crosstalk provides a unifying conceptual framework linking molecular mechanisms with clinical outcomes and represents a critical and clinically translatable foundation for next-generation preventive and therapeutic strategies.

5. Conclusions

Neuro-endocrine-immune (NEI) crosstalk constitutes a fundamental system-level regulatory framework underlying the development and progression of chronic diseases. The integration of neural, endocrine, and immune signaling pathways governs both physiological homeostasis and maladaptive responses, with dysregulation of this axis emerging as a common denominator across diverse disease entities [1,3,5,17,18].

A central conclusion of this review is that chronic diseases should be understood not as isolated organ-specific conditions, but as manifestations of multi-system regulatory imbalance involving interconnected biological networks. Convergent mechanisms-including chronic low-grade inflammation, dysregulated stress responses, and immune dysfunction-shape disease susceptibility, progression, and chronicity across systems [12,15,17,19].

This integrative perspective provides a unifying model linking cardiovascular, metabolic, neurodegenerative, psychiatric, and oncological disorders through shared regulatory pathways [7,9,19,30,31].

From a translational perspective, NEI crosstalk enables the identification of clinically actionable, multi-dimensional biomarker signatures integrating immune, neuroendocrine, metabolic, and autonomic parameters. Such approaches have the potential to improve early detection, risk stratification, and monitoring of disease trajectories [17,21,27].

Targeting interconnected regulatory pathways-including stress modulation, immune regulation, metabolic balance, microbiota dynamics, and environmental sensing mechanisms such as the aryl hydrocarbon receptor-represents a promising strategy for integrative prevention and therapy [22,24,27,33].

These findings align with the principles of systems medicine and predictive, preventive, personalized, and participatory (P4) medicine, emphasizing proactive and individualized disease management [36,37].

Importantly, the implementation of NEI-oriented strategies in clinical practice may enable earlier identification of at-risk individuals and more precise, mechanism-based interventions, thereby improving long-term outcomes.

Neuro-endocrine-immune crosstalk thus emerges as a unifying biological paradigm linking molecular mechanisms with clinical outcomes and provides a critical, translationally relevant foundation for next-generation strategies in chronic disease prevention and management. Further research should focus on validating integrative biomarker panels and translating systems-level insights into clinically applicable frameworks.

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