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Review Paper

Chronic Spontaneous Urticaria: Immune Dysregulation, Microbiome Imbalance, and Neuroinflammation

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ABSTRACT

Chronic spontaneous urticaria (CSU) is a complex dermatological disorder that affects both adults and children, with a higher prevalence among women, significantly impacting quality of life. Characterized by persistent itchy wheals and angioedema lasting over six weeks without a clear trigger, CSU is driven by a multifaceted interplay of immune dysfunction, neuroimmune interactions, and gut microbiome imbalances. While mast cells and basophils play a central role, recent insights highlight autoantibodies, nerve-mediated inflammation, and microbiome dysbiosis as critical factors influencing disease progression. This review explored emerging autoimmune mechanisms, including IgG autoantibodies targeting IgE receptors, non-IgE-dependent mast cell activation via MRGPRX2, and increased Spleen tyrosine kinase (SYK) expression, alongside the gut-skin connection and neuropeptide-driven inflammation. We examined how microbiome alterations affect immune homeostasis and how neuropeptides, like substance P (SP) and calcitonin gene-related peptide (CGRP), contribute to CSU severity. By integrating established immunological principles with recent neurobiological discoveries, this review provides fresh insights into CSU pathogenesis, paving the way for personalized therapeutic strategies that target immune modulation, microbiome restoration, and neuroimmune regulation.

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Introduction

Although the pathophysiology of chronic spontaneous urticaria (CSU) has not been fully understood, mast cells and basophils play a contributory role in disease pathogenesis. However, other molecules, such as eosinophils and neutrophils, also play a role in the disease pathogenesis. The visible signs of urticaria arise when blood vessels become more permeable, a change driven by mast cells releasing stored mediators, such as histamine, tryptase, and leukotrienes, along with subsequent cytokine production. The current research assessed how mast cells are triggered by antigens in the bloodstream, with mouse studies suggesting that CD301b+ dermal dendritic cells may be the initial antigen samplers that subsequently transfer these signals to nearby mast cells through the release of microvesicles [1]. However, most cases of chronic urticaria do not have an identified trigger, rendering them idiopathic. Mast cells can get activated through immunologic and nonimmunologic pathways. Figure 1 provides a schematic overview of CSU's multifactorial pathogenesis, illustrating the interplay of immune dysregulation, gut microbiome imbalances, and neuroimmune interactions, with arrows highlighting the dynamic connections between immune cells, microbial metabolites, and neural pathways. A PubMed search was conducted for articles published between 1990 and March 2024 using keywords related to CSU, mast cell activation, autoimmunity, neuroimmune signaling, and gut microbiota. Additional references were identified through manual screening of bibliographies from relevant publications. Included studies were English-language publications that addressed mechanisms underlying CSU, particularly those involving immune dysregulation, neuropeptides, and microbiome interactions. Articles focused solely on treatment outcomes, case reports, or lacking methodological clarity were excluded.

How Immunological Triggers Activate Mast Cells in CSU

The initial evidence of immunologically driven mast cell activation was obtained by observing wheal formation at the site of an intradermal injection of the patient's serum, a procedure now known as the autologous serum skin test (ASST). A substantial proportion of CSU cases are believed to result from immunologically driven activation of mast cells or basophils. This activation is primarily mediated through two distinct endotypes: Type I autoallergic CSU, characterized by IgE autoantibodies against autoantigens such as thyroid peroxidase (TPO), or Interleukin 24 (IL-24), and type IIb autoimmune CSU, driven by IgG autoantibodies targeting IgE or its high-affinity receptor FcεRI [2, 3]. While type I autoallergic CSU appears to be more prevalent, type IIb autoimmune CSU is estimated to affect fewer than 10% of patients when strict diagnostic criteria are applied [2]. Emerging evidence suggests that these endotypes may overlap in some individuals, underscoring the complexity of CSU pathogenesis and the need for refined diagnostic markers [4].

In the early 1990s, research suggested that IgE autoantibodies play a crucial role in the development of CSU. This insight, supported by subsequent studies, paved the way for a groundbreaking randomized controlled trial that tested omalizumab, an anti-IgE antibody, in CSU patients who exhibited IgE reactivity to TPO, a frequently implicated autoallergen. Named the X-CUISITE trial, the study found that omalizumab prompted a rapid and impressive complete response in 70% of patients, outperforming outcomes in later trials. Subsequent research into the distribution, function, and targets of IgE autoantibodies has reinforced these findings and culminated in the classification of a type I autoimmune (or auto-allergic) endotype of CSU.

IgG autoantibodies to high-affinity receptor FcεRI and/or IgE were detected more than 30 years ago; today, patients with these autoantibodies are classified as having type IIb autoimmune CSU. The international PURIST (profiling urticaria for the identification of subtypes) study was the first large-scale investigation on CSU patients to evaluate three key features of type IIb autoimmune CSU: A positive ASST, the detection of IgG autoantibodies against either FcεRI or IgE, and a positive basophil test (using either the basophil activation test or the basophil histamine release assay). This study revealed that under 10% of CSU patients exhibit type IIb aiCSU, with these individuals typically experiencing more severe symptoms, reduced total IgE levels, and increased TPO autoantibodies. Nevertheless, there is a significant challenge in performing these three tests simultaneously in the laboratory due to their high costs and limited availability. Scientists are working to find more accessible biomarkers to improve the diagnosis and understanding of the condition. One promising avenue is analyzing the anti-TPO/IgE ratio, which recent studies suggest could be a more upfront and effective alternative to current testing methods [5].

Meanwhile, ongoing research indicates that IgM and IgA autoantibodies targeting FcεRI may contribute to the disease's progression, adding another layer of complexity to the underlying mechanisms of CSU [6]. In addition, over the past decade, extra markers, such as nocturnal symptoms, eosinopenia, and low total IgA, have been identified, while recent findings highlight that type IIb aiCSU often responds poorly or only slowly to standard therapies, like antihistamines and omalizumab.

Concerning the potential overlap between these two endotypes, Asero et al. [7] investigated the simultaneous presence of IgG and IgE autoantibodies against IgE receptors (FcεRI and FcεRII), tissue factor, and thyroglobulin. Their study revealed that more than half of CSU patients possess both types of autoantibodies targeting these molecules. Furthermore, biomarkers of type IIb aiCSU, such as basophil activation tests and indicators of auto-allergic CSU, like IgE autoantibodies against IL-24, have been repeatedly linked to heightened disease activity and basopenia. Additional research has shown that CSU patients frequently co-express both IgE and IgG autoantibodies against TPO, with distinct autoantibody profiles correlating with disease severity, reduced basophil counts, and a favorable response to omalizumab, further underscoring the complex autoimmune nature of this condition.

Spleen tyrosine kinase (SYK) overexpression and its impact on mast cell signaling

CSU is underpinned by dysregulated activation of inflammatory cells, chiefly mast cells and basophils, through intricate intracellular signaling mechanisms. In mast cells, the engagement of the high-affinity IgE receptor (FcεRI) comprising an α-subunit that binds IgE and β/γ subunits containing ITAMs triggers phosphorylation events that recruit SYK [8]. SYK then initiates downstream cascades, including the PI3K pathway, which ultimately leads to the degranulation process characterized by the release of histamine, lipid mediators, and cytokines [9]. Notably, mast cells from CSU patients, particularly those classified as responders (with degranulation activity exceeding 10%), present higher SYK expression in contrast to non-responders, wherein phosphatase activity (such as through SHIP proteins) dampens SYK activation and histamine release [10].

Similarly, basophils, which share the FcεRI with mast cells, contribute to CSU pathogenesis by migrating from the bloodstream to sites of wheals in response to chemotactic cues, like MCPs [11-13] and a PGD2-dependent pathway [11]. Once at the site, basophils release mediators, such as histamine and leukotriene C4 [14], with their intracellular signaling also governed mainly by SYK activation. In CSU patients, basophils can be categorized into two functional phenotypes [15]: In one, high SYK levels facilitate robust histamine degranulation akin to that observed in healthy cells, while in the other phenotype, dephosphorylation of SYK by excess phosphatases curbs histamine release. Studies have highlighted a reduction in SHIP levels within the basophils of individuals affected by CSU. Additionally, investigations into mast cell responses have shown that in patients exhibiting histamine release upon anti-IgE stimulation, SHIP-2 expression is diminished, while SYK levels are increased [10, 16].

SYK inhibitors have been identified as promising candidates for the future treatment of CSU. Among these, GSK2646264, a selective SYK inhibitor, is currently undergoing evaluation in a clinical trial to assess its potential effectiveness in managing CSU symptoms. These findings highlight the potential therapeutic value of targeting this pathway to alleviate symptoms [17].

How non-immunological triggers activate mast cells in CSU

Although IgE and IgG-dependent stimulation cause degranulation in mast cells, these cells can also be activated by mechanisms independent of these pathways. Cutaneous mast cells can be degranulated by polybasic agents, such as Poly-L-lysine or the 80/48 combination, through the expression of the G protein-coupled receptor associated with the *X2* gene (*MrgX2*) [18]. Studies indicate that CSU patients exhibit higher concentrations of MRGPRX2 ligands, including substance P (SP) and vasoactive intestinal peptide (VIP), in their skin compared to healthy individuals. Furthermore, mast cells activated by anti-IgE release cortistatin (CST), a potent MRGPRX2 agonist, which triggers a concentration-dependent degranulation process in human skin mast cells [19]. Mast cells also express neuropeptide receptors, including neurokinin receptors 1 and 2 (NK1R and NK2R), the calcitonin gene-related peptide (CGRPR) receptor, as well as neurotrophin receptors and tropomyosin-related kinases (TrkA, TrkB, TrkC) [18]. Neuropeptides, like SP, VIP, and somatostatin, can trigger both mast cell degranulation and cytokine production. Despite the wide range of neuropeptide receptors present in mast cells, MrgX2 appears to be the most critical receptor for their activation. In CSU, neurogenic inflammation may arise due to heightened CST and neuropeptide production by mast cells and sensory nerves, leading to a continuous

cycle of mast cell activation. This activation further attracts inflammatory cells, such as eosinophils, which release MRGPRX2 ligands, including major basic protein (MBP) and eosinophil peroxidase (EPO), ultimately stimulating histamine release through MRGPRX2 signaling [20].

Protease-activated receptors (PARs) belong to the G protein-coupled receptor family and are activated when their extracellular domain is cleaved by specific serine proteases, such as trypsin, tryptase, and activated coagulation factors. These receptors are expressed in various cell types, including mast cells, platelets, endothelial cells, and neurons. In mammals, there are four types of these receptors (PAR-1, PAR-2, PAR-3, and PAR-4). Some studies have highlighted mast cell activation via PAR2 agonists, such as trypsin. Furthermore, an increased expression of PAR2 in mast cells has been observed in urticarial lesions compared to healthy skin. Additionally, elevated mRNA expression of PAR-1 and PAR-2 in human mast cells has been reported, despite the absence of histamine release in response to PAR-1 and PAR-2 agonists [21].

Studies have shown that CSU patients exhibit reduced plasma levels of IL-35 and vitamin D. Consequently, targeting pathways associated with these molecules may provide a promising approach for CSU treatment. Furthermore, several cytokines and receptors, including IL-4, IL-5, IL-13, TSLP, C5a, the C5a receptor (C5aR), and chemokine receptor 3 (CCR3), are currently being investigated in clinical trials as potential therapeutic agents [21, 22]. These findings emphasize that the underlying mechanisms of CSU are more complex than previously believed. There is a possibility that autoantibodies against mast cell-activating receptors, such as C5a or MRGPRX2, exist; however, this has yet to be confirmed through research [2] (Table 1).

The Role of the Gut Microbiome in CSU

The gut microbiota is a vast and interconnected ecosystem within the body, essential for maintaining overall health. It plays a key role in digestion, supports immune function, and helps regulate various physiological processes by ensuring a balanced mix of beneficial microorganisms. Disruptions in this intricate network have been linked to multiple health conditions, including allergic diseases, like asthma [24], food allergies [25], and atopic dermatitis [26]. Recent studies have focused on the role of the gut microbiome in CSU pathogenesis, reporting changes in gut microbiota in CSU patients. A decrease in microbial diversity in CSU patients has been reported in many studies. This decline leads to dysbiosis, characterized by a reduction in beneficial bacterial species, such as *Faecalibacterium prausnitzii*, Bacteroidetes, Firmicutes, and Lactobacillus, while opportunistic bacteria, like Enterobacteriaceae and Proteobacteria, proliferate [27]. For instance, a study [28] examined gut dysbiosis, revealing reduced bacterial diversity and lower levels of beneficial short-chain fatty acid (SCFA)-producing bacteria, such as *Roseburia hominis*. Conversely, opportunistic pathogens, like *Klebsiella pneumoniae*, were elevated, which are harmful to intestinal wall integrity. These microbial alterations were associated with increased blood lipopolysaccharide (LPS) levels, immune dysregulation, and higher mast cell activity, suggesting that gut microbiota imbalances contribute to CSU pathogenesis. Moreover, Wang et al. [29] reported decreased bacterial diversity in CSU patients by increased levels of unidentified Enterobacteriaceae and reduced levels of beneficial bacteria, such as Bacteroides, Faecalibacterium, Bifidobacterium, and unidentified Ruminococcaceae.

These microbial imbalances may contribute to a Th1/Th2/Th17 cytokine imbalance, disrupting immune homeostasis and triggering excessive inflammation, which can lead to symptoms of CSU.

Microbiome dysbiosis and its potential link to immune system dysregulation in CSU

One of the key mechanisms by which the gut microbiome influences CSU is through the regulation of SCFAs, particularly butyrate [28], which plays a vital role in promoting Treg cell differentiation and suppressing inflammation. CSU patients exhibit reduced levels of butyrate-producing bacteria, such as *Subdoligranulum* and *Ruminococcus bromii*, resulting in impaired Treg cell function [30]. Additionally, CSU patients exhibit alterations in unsaturated fatty acids, such as docosahexaenoic acid and arachidonic acid [29], which are crucial for immune balance.

The metabolomic profile of CSU patients further supports the connection between gut microbiota and disease severity. Studies reveal that changes in serum metabolites related to butanoate metabolism and immune modulation correlate with microbiome dysbiosis. Metabolomics research has highlighted significant differences in butanoate metabolism between individuals with CSU and those without the condition. Butyrate plays a crucial role in maintaining intestinal epithelial integrity and contributes to immune tolerance within the gut [31]. Research has shown that children with asthma tend to have lower butyrate levels, which appear to be inversely linked to

Table 1. Non-immunological receptors activating immune cells in CSU

Receptor	Type	Activation Mechanism	Key Ligands	Impacted Cells	Ref.
MRGPRX2	G protein-coupled receptor (GPCR)	Activated by polybasic agents (Poly-L-lysine, 48/80), neuropeptides, and CST released after anti-IgE activation	SP, VIP, CST, MBP, and EPO	Mast cells and eosinophils	[18-20]
NK1R, NK2R	Neuropeptide receptors	Activated by neuropeptides that trigger mast cell degranulation and cytokine release	SP and neurokinins	Mast cells	[18]
CGRPR	GPCR Receptor	Involved in neurogenic inflammation, responding to sensory neuron-derived peptides	CGRP	Mast cells and sensory neurons	[18]
TrkA, TrkB, TrkC	Neurotrophin receptors	Activated by NGFs, contributing to mast cell activation	Neurotrophins (NGF and BDNF)	Mast cells and sensory neurons	[18]
PARs (PAR-1, PAR-2, PAR-3, PAR-4)	GPCRs	Cleaved by serine proteases, like trypsin, tryptase, and coagulation factors, triggering cellular activation	Trypsin, tryptase, and coagulation factors	Mast cells, platelets, endothelial cells, and neurons	[21]
CRH type I	G protein-coupled receptor (GPCR)	Activated by CRH, influencing stress response and immune modulation	CRH, and urocortins (UCN1, UCN2, and UCN3)	Mast cells, neurons, and immune cells	[23]

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serum IgE concentrations [32]. Reduced butyrate production may disrupt the intestinal epithelial barrier, potentially influencing allergen absorption and immune responses related to allergic asthma. Recent research indicates a decline in serum glutamate and succinic acid levels, both of which are essential for butanoate metabolism [29]. At the same time, a noticeable reduction in beneficial gut bacteria, such as *Bifidobacterium* and *Faecalibacterium*, suggests a broader microbial imbalance that may influence overall health. Meanwhile, a rise in unidentified Enterobacteriaceae correlates negatively with glutamate levels.

Role of gut microbiota in CSU treatment

Certain bacterial strains, such as *Lachnospira*, have been identified as potential biomarkers for predicting the efficacy of antihistamine treatments in CSU [33]. Patients with lower levels of *Lachnospira* tend to have poorer responses to conventional antihistamine therapy, highlighting the potential of microbiome-targeted interventions as therapeutic strategies.

Given this growing evidence, modulating the gut microbiome through probiotics, prebiotics, and dietary interventions may offer new avenues for CSU treatment. Some clinical studies have demonstrated that probiotic supplementation, including strains, such as *Bifidobacterium breve* and *Lactobacillus salivarius*, can help reduce inflammation and improve CSU symptoms [34]. On the other hand, the combination of probiotics and antihistamines shows no significant difference in efficacy compared to antihistamines alone; however, some patients experienced lower CSU severity, reduced itching, and fewer hives [34, 35].

Further research with larger cohorts is necessary to validate these findings and optimize microbiome-based therapies. Understanding the intricate relationship between gut microbiota and CSU pathogenesis may pave the way for personalized treatments that enhance symptom management and patient quality of life (Table 2).

Neuroimmune Interactions in CSU

Mast cells can become activated independently of FcεRIs by other biological factors, such as neuropeptides. Neuropeptides are small protein molecules produced and released by neurons, and can act as neurotransmitters or neuromodulators in the nervous system. They also interact with mast cells and induce their degranulation by different types of neuropeptides, especially SP, CGRP, and neuropeptide Y (NPY), which are secreted by free nerve endings in response to a range of chemical and physical triggers. These molecules play a crucial role in signaling pathways related to pain, inflammation, and neural communication. A possible relationship between SP and chronic urticaria has been reported [37]. The variation in this substance's serum levels remains a topic of debate, as evidence regarding whether they rise or fall is

Table 2. Gut microbiota alterations and their influence on immune balance

Bacteria	Role in Gut & Immune Function	Impact on CSU	Ref.
F. prausnitzii	Anti-inflammatory; produces SCFAs, particularly butyrate	Reduced levels in CSU, linking to inflammation	[25, 27]
Bacteroidetes	Supports microbial diversity & immune balance	Reduced levels cause gut dysbiosis	[25, 27]
Firmicutes	Helps produce SCFAs and strengthens the gut barrier	Reduced levels impair intestinal integrity	[25, 27]
Lactobacillus	Regulates immune responses and reduces inflammation	Reduced levels linked to an immune imbalance	[25, 27]
Roseburia hominis	Producer of SCFAs (especially butyrate), maintaining gut health	Reduced levels in CSU, worsening symptoms	[28]
Ruminococcaceae (unidentified strain)	Regulates immune responses and supports SCFA metabolism	Reduced levels in CSU, increasing inflammation	[29]
Subdoligranulum	A butyrate producer essential for Treg function	Low levels disrupt immune tolerance	[30]
R. bromii	Aids in fiber digestion and supports gut immunity	Reduced levels in CSU, affecting immune modulation	[30]
B. breve	Serving as a probiotic strain that improves gut health	Supplementation may reduce CSU symptoms	[34]
L. salivarius	Supports the gut barrier and immune modulation	Helps alleviate CSU-related inflammation	[34]
Lachnospira	Potential biomarker for antihistamine efficacy	Lower levels linked to poor drug response	[36]
Enterobacteriaceae	An opportunistic pathogen that promotes inflammation	Increased levels in CSU, worsening immune imbalance	[27]
Proteobacteria	Associated with gut dysbiosis and inflammation	Elevated levels in CSU, linking to immune dysfunction	[25, 27]
K. pneumoniae	Disrupts intestinal integrity, increases LPS levels	Higher abundance in CSU patients	[28]
Unidentified Enterobacteriaceae	Negatively correlates with beneficial metabolites	Elevated in CSU and worsens microbiome dysbiosis	[27]

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inconclusive. One important receptor for SPs is NKR1 (neurokinin receptor 1), which is mainly expressed in the skin and the central nervous system [38]. Another vital receptor for this substance is the G protein-coupled receptor X2 (MRGPRX2) on mast cells, which likely causes mast cell degranulation. This receptor in humans is triggered by cationic ligands, which encompass a wide variety of compounds, including antimicrobial host defense peptides, neuropeptides, and eosinophil granule proteins that have been reported to be upregulated in patients with severe CSU [39]. Some data indicate a rise in SP serum levels in CSU patients compared to healthy controls, further highlighting the potential role of SP-MRGPRX2-MC pathway in the development and progression of CSU [37, 40-42]. However, Boyvadoglu et al. [43] reported a decrease in SP levels in CSU patients compared to healthy controls. Further research must be performed to elucidate the precise role of this substance in the pathogenesis of CSU.

NPY is another neuropeptide that plays a key role in triggering itch and stimulates mast cell activity, enhancing processes, such as cell adhesion, directional movement (chemotaxis), engulfing of particles (phagocytosis), lymphocyte function, antibody generation, and cytokine release. Typically, NPY is secreted by neurons when they experience stress, and research indicates that lower levels of NPY in the blood tend to correspond with more intense itch sensations [44]. Although there are only a few studies concerning the evaluation of this factor in CSU patients, further research is needed on this neuropeptide. Boyvadoglu et al. [43] reported a lower level of NPY in CSU patients compared to healthy controls, and they observed no significant change in its level after omalizumab treatment. One study reported a decrease in the level of this factor after treatment with antihistamines [45]. Moreover, Basak et al. [40] evaluated serum neuropeptide levels in 57 patients with chronic urticaria compared to 46 healthy controls and identified NPY as a key biomarker in predicting the outcome of the autologous plasma skin test (APST).

CGRP is another important neuropeptide that plays a key role in neurogenic inflammation, pain modulation, and vasodilation. Regarding mast cells, CGRP has been shown to influence their activation and degranulation, contributing to inflammatory responses. It was found to significantly enhance the wheal and flare reactions in

Table 3. Neuropeptides in CSU: Roles, impact, and serum changes after treatment

Neuropeptide	Function	Impact on CSU	Serum Changes After Treatment	Ref.
SP	A neurotransmitter involved in pain, inflammation, and mast cell degranulation	Interacting with NKR1 and MRGPRX2, leading to mast cell activation	Conflicting findings—some studies report an increase, while others show no change after antihistamines or omalizumab	[23, 37, 40-43, 45, 53]
NPY	Regulates itch, mast cell activity, and immune functions	Lower levels in CSU patients and correlation with severe itching	No significant change after omalizumab, but may decrease after antihistamine treatment	[40, 43, 44]
CGRP	A key player in neurogenic inflammation, vasodilation, and mast cell activation	Enhancing wheal and flare reactions and contributing to mast cell degranulation	An increase after antihistamines and omalizumab, possibly due to compensatory mechanisms	[43, 45-47, 53]
CRH	Released in response to stress	Triggers mast cell degranulation, worsening CSU symptoms	No direct studies on CRH serum levels in CSU	[23]
NGF	Regulates sensory nerve activity and neurogenic inflammation	Elevated NGF levels are linked to itching and pain sensitivity	No direct studies on NGF serum levels in CSU	[18, 50]

IMMUNOREGULATION

individuals with CSU when injected intradermally [46]. Previous studies have highlighted increased expression of CGRP in the lesional skin of CSU patients compared to non-lesional skin [47]. Interestingly, findings have reported increased serum CGRP levels after H1 antihistamine and omalizumab treatment [43, 45]. The increase in CGRP levels after treatment may be counterintuitive; however, it could be due to the fact that these treatments do not fully counteract the underlying neuroimmune mechanisms driving CGRP expression. This further emphasizes that CSU is not solely histamine-driven and that other mediators also play a role (Table 3).

Further studies on neuropeptides can help identify whether they are viable targets for future treatment.

Stress-induced mast cell activation and its implications for CSU severity

Growing research indicates that heightened psychological stress levels can significantly worsen the pathogenic symptoms of CSU. Furthermore, excessive stress may not only aggravate existing CSU cases but also contribute to an increased risk of developing the condition. While research suggests a connection between psychological strain and CSU symptoms, the underlying biological mechanisms are not yet fully understood.

The brain-skin connection, involving local neuro-immune endocrine pathways, may play a crucial role in the development and worsening of stress-related allergic and inflammatory skin conditions. This theory is supported by numerous studies examining the impact of stress on the neuroendocrine and immune systems, particularly in conditions, such as psoriasis and atopic dermatitis [48, 49]. Stress-triggered biological responses may play a key role in worsening and prolonging inflammatory skin conditions. The body's stress system relies on a complex network involving endocrine and neural pathways. Endocrine pathways include circulating hormones of the hypothalamic-pituitary-adrenal–adrenal (HPA) axis, and neural pathways are related to the sympathetic system, which helps regulate both physical and psychological responses to stress.

Stress-related neurohormones, like corticotropin-releasing hormone (CRH), arginine-vasopressin, adrenocorticotropic hormone, glucocorticoids, norepinephrine, and epinephrine, primarily drive this process. Beyond these, additional mediators, including nerve growth factor (NGF) and cytokines, significantly influence neurological and immune functions. In the skin, sensory nerve fibers extend and branch toward regions with elevated NGF levels. This factor regulates sensitivity thresholds in interactions between mast cells and nerve fibers [18]. Under pathological conditions, heightened reactivity leads to increased skin sensitivity, amplifying neurogenic flare responses, itching, and pain. Studies show elevated NGF levels in individuals with inflammatory skin conditions, such as psoriasis [50], reinforcing the link between stress, immune system imbalance, and chronic inflammation.

Regarding the association between stress and CSU severity, the skin environment contains numerous nerve fibers that produce various neuropeptides. These nerve fibers are near mast cells, facilitating neuroimmune interactions. These nerve fibers can be activated through stress stimulation and subsequently release numerous neuropeptides, which are stored within the cytoplasmic

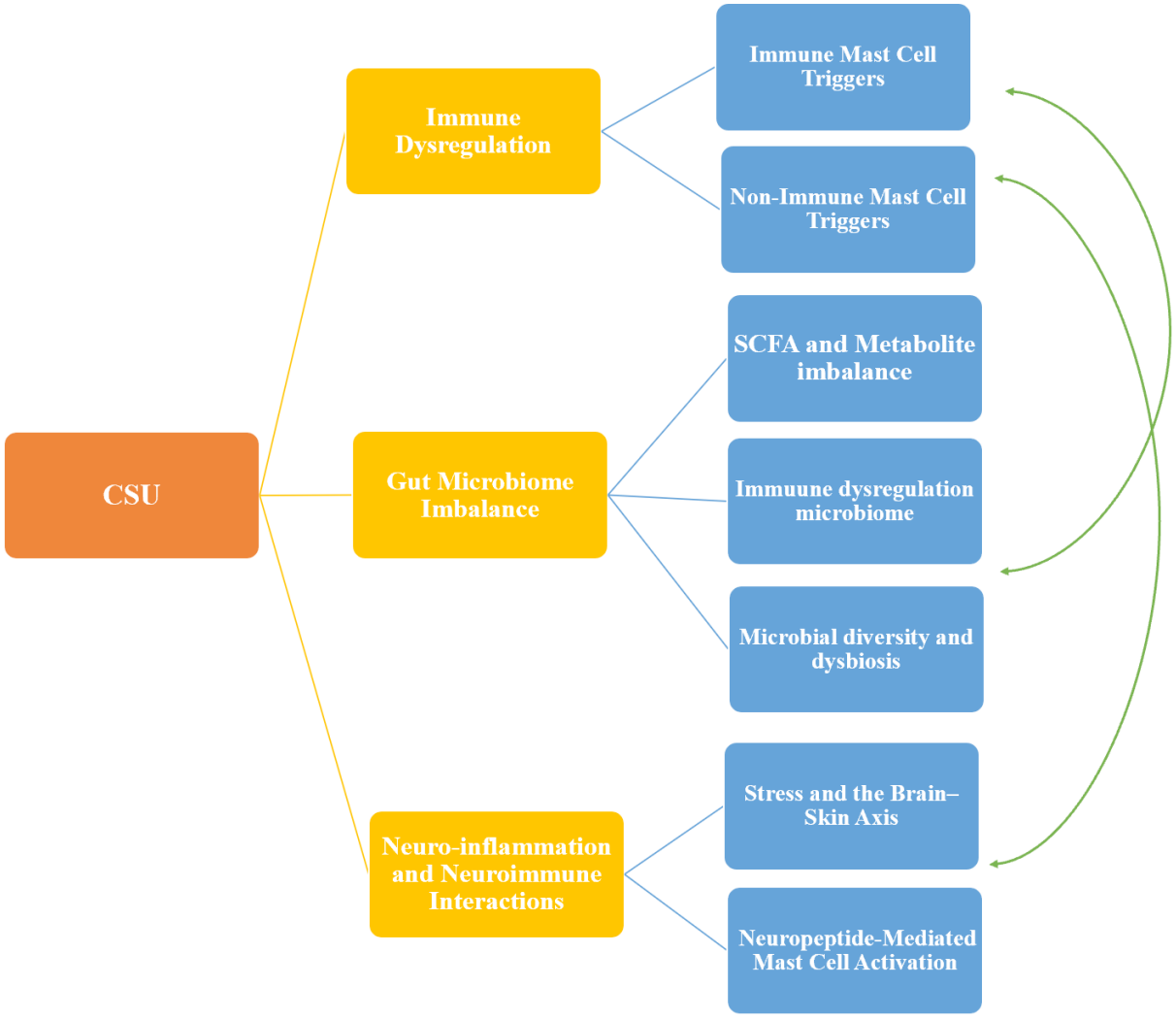

Figure 1. Schematic overview of the multifactorial pathogenesis of CSU

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Note: The diagram illustrates three major interconnected domains contributing to CSU: Immune Dysregulation, Gut Microbiome Imbalance, and Neuroimmune Interactions. Each domain branches into key mechanistic subcategories, including immune and non-immune mast cell triggers, microbial dysbiosis and metabolite imbalance, and neuropeptide-driven inflammation. Arrows indicate the dynamic interplay between immune cells, microbial metabolites, and neural pathways, highlighting the complex and overlapping nature of CSU pathophysiology.

vesicles of nociceptive neurons. These molecules travel antidromically from axon terminals to the site of stimulation [51-53]. Neuropeptides trigger mast cell degranulation, leading to the release of histamine, tryptase, and NGF, as well as peptidergic C fibers containing proinflammatory neuropeptides, like SP and CGRP. The ongoing interaction between mast cells and sensory fibers amplifies neurogenic inflammation and itching, creating a cycle that reinforces mast cell activation [51, 52, 54]. It has been reported that emotional stress may trigger urticarial symptoms through mast cell degranulation via an IgE-independent pathway involving G-protein-coupled receptors [18, 55] and CRH receptors type I. Various neuropeptides, such as peripheral CRH, SP, and CGRP, are released from postganglionic sympathetic and sensory neurons in response to stress or inflammatory signals, thereby initiating these processes [23].

Serum neuropeptides change in CSU patients after treatment

Although there are not many studies on triggering neuropeptides for CSU treatment, Basak et al. [45] reported increased CGRP levels and no change in SP levels after antihistamine treatment. Another study reported the same result following omalizumab treatment [53]. In a study performed by Boyvadoglu et al. [43], increased levels of SP and CGRP were reported. This rise might be due to compensatory mechanisms or incomplete sup-

pression of inflammation. Further research is needed to determine the underlying cause of this increase. Interestingly, SP antagonists have shown an antipruritic effect on both acute and chronic pruritus in several pruritic conditions [56]. Moreover, spantide, an SP antagonist, has been reported as an inhibitor of both immediate and delayed-type cutaneous hypersensitivity reactions [57]. Studies on NK-1 receptor antagonists are also underperforming [58]. However, we could not find any studies concerning the direct target of neuropeptides in CSU patients (Table 3).

Conclusion

CSU is a condition driven by a complex mix of immune system dysfunction, neuroimmune interactions, and gut microbiome imbalances. While IgE and IgG autoantibodies fuel mast cell activation and histamine release, research shows that neuropeptides, like SP, CGRP, and NPY, along with PARs and MRGPRX2, play a significant role in symptom progression, especially in response to stress-related triggers. These pathways create a cycle of inflammation that makes CSU harder to manage with traditional approaches.

The gut microbiome also plays a key role in CSU, as changes in bacterial diversity can affect the body's ability to regulate inflammation. Patients with CSU often experience a decline in beneficial SCFA-producing bacteria, while opportunistic strains, such as Enterobacteriaceae and *K. pneumoniae*, thrive, thereby exacerbating immune dysfunction. Restoring gut balance through the use of probiotics or dietary adjustments may reduce CSU severity and improve long-term outcomes.

Stress plays an important role in triggering mast cell activity and neuroimmune responses, thereby amplifying symptoms, such as itching, inflammation, and increased skin sensitivity. When stress hormones flood the body, they activate nearby nerve fibers, which in turn stimulate mast cells, perpetuating the cycle of irritation and discomfort. This explains why CSU flare-ups often coincide with periods of emotional strain or physical exhaustion, reinforcing the deep connection between the nervous system and skin health.

As scientific research continues to shed light on the complexities of CSU, treatment strategies must expand beyond standard antihistamines and biologics to address the underlying neuroimmune and inflammatory pathways that drive the condition. A more holistic, personalized approach may be the key to long-term symptom management and improving patient outcomes. Addressing immune dysfunction, gut microbiome health, and neuroimmune regulation will be key to developing more personalized therapies. New approaches, such as SYK inhibitors, microbiome-based interventions, and neuropeptide-targeting therapies, offer hope for patients seeking long-term relief from this challenging condition.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Conflicts of interest

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References

[1] Choi HW, Suwanpradid J, Kim IH, Staats HF, Haniffa M, MacLeod AS, et al. Perivascular dendritic cells elicit anaphylaxis by relaying allergens to mast cells via microvesicles. Science. 2018; 362(6415):eaao0666. [DOI:10.1126/science.aao0666] [PMID]

[2] Kolkhir P, Munoz M, Asero R, Ferrer M, Kocaturk E, Metz M, et al. Autoimmune chronic spontaneous urticaria. The Journal of Allergy and Clinical Immunology. 2022; 149(6):1819-31. [DOI:10.1016/j.jaci.2022.04.010] [PMID]

[3] Larenas-Linnemann D. Biomarkers of autoimmune chronic spontaneous urticaria. Current Allergy and Asthma Reports. 2023; 23(12):655-64. [DOI:10.1007/s11882-023-01117-7] [PMID]

[4] Sella JA, Ferriani MPL, Melo JML, Trevisan Neto O, Zanetti MET, Cordeiro DL, et al. Type I and type IIb autoimmune chronic spontaneous urticaria: Using common clinical tools for endotyping patients with CSU. The Journal of Allergy and Clinical Immunology. Global. 2023; 2(4):100159. [DOI:10.1016/j.jacig.2023.100159] [PMID]

[5] Kolkhir P, Kovalkova E, Chernov A, Danilycheva I, Krause K, Sauer M, et al. Autoimmune chronic spontaneous urticaria detection with IgG anti-TPO and total IgE. The Journal of Allergy and Clinical Immunology. In practice. 2021; 9(11):4138-46 e8. [DOI:10.1016/j.jaip.2021.07.043] [PMID]

[6] Sauer M, Scheffel J, Frischbutter S, Kolkhir P, Xiang YK, Siebenhaar F, et al. Lower IgA levels in chronic spontaneous urticaria are associated with lower IgE levels and autoimmunity. Frontiers in Immunology. 2021; 12:657211. [DOI:10.3389/fimmu.2021.657211] [PMID]

[7] Asero R, Marzano AV, Ferrucci S, Lorini M, Carbonelli V, Cugno M. Co-occurrence of IgE and IgG autoantibodies in patients with chronic spontaneous urticaria. Clinical and Experimental Immunology. 2020; 200(3):242-9. [DOI:10.1111/cei.13428] [PMID]

[8] Turner H, Kinet JP. Signalling through the high-affinity IgE receptor Fc epsilonRI. Nature. 1999; 402(6760 Suppl):B24-30. [DOI:10.1038/35037021] [PMID]

[9] Bracken SJ, Abraham S, MacLeod AS. Autoimmune Theories of Chronic Spontaneous Urticaria. Frontiers in Immunology. 2019; 10:627. [DOI:10.3389/fimmu.2019.00627] [PMID]

[10] Saini SS, Paterniti M, Vasagar K, Gibbons SP Jr, Sterba PM, Vonakis BM. Cultured peripheral blood mast cells from chronic idiopathic urticaria patients spontaneously degranulate upon IgE sensitization: Relationship to expression of Syk and SHIP-2. Clinical Immunology. 2009; 132(3):342-8. [DOI:10.1016/j.clim.2009.05.003] [PMID]

[11] Gimenez-Arnau AM, DeMontojoye L, Asero R, Cugno M, Kulthanan K, Yanase Y, et al. The pathogenesis of chronic spontaneous urticaria: The role of infiltrating cells. The Journal of Allergy and Clinical Immunology. In Practice. 2021; 9(6):2195-208. [DOI:10.1016/j.jaip.2021.03.033] [PMID]

[12] Kuna P, Reddigari SR, Rucinski D, Oppenheim JJ, Kaplan AP. Monocyte chemotactic and activating factor is a potent histamine-releasing factor for human basophils. The Journal of Experimental Medicine. 1992; 175(2):489-93. [DOI:10.1084/jem.175.2.489] [PMID]

[13] Kaplan AP, Kuna P, Reddigari S, Rucinski D, Baeza M, Oppenheim JJ, et al. Relationship of histamine-releasing factors to the human intercrine/chemokine group of cytokine-like molecules. International Archives of Allergy and Immunology. 1992; 99(2-4):311-5. [DOI:10.1159/000236271] [PMID]

[14] Oliver ET, Sterba PM, Devine K, Vonakis BM, Saini SS. Altered expression of chemoattractant receptor-homologous molecule expressed on T(H)2 cells on blood basophils and eosinophils in patients with chronic spontaneous urticaria. The Journal of Allergy and Clinical Immunology. 2016; 137(1):304-6 e1. [DOI:10.1016/j.jaci.2015.06.004] [PMID]

[15] Eckman JA, Hamilton RG, Gober LM, Sterba PM, Saini SS. Basophil phenotypes in chronic idiopathic urticaria in relation to disease activity and autoantibodies. The Journal of Investigative Dermatology. 2008; 128(8):1956-63. [DOI:10.1038/jid.2008.55] [PMID]

[16] Vonakis BM, Gibbons S Jr, Sora R, Langdon JM, MacDonald SM. Src homology 2 domain-containing inositol 5′ phosphatase is negatively associated with histamine release to human recombinant histamine-releasing factor in human basophils. The Journal of Allergy and Clinical Immunology. 2001; 108(5):822-31. [DOI:10.1067/mai.2001.119159] [PMID]

[17] Dickson MC, Walker A, Grattan C, Perry H, Williams N, Ratia N, et al. Effects of a topical treatment with spleen tyrosine kinase inhibitor in healthy subjects and patients with cold urticaria or chronic spontaneous urticaria: Results of a phase 1a/b randomised double-blind placebo-controlled study. British Journal of Clinical Pharmacology. 2021; 87(12):4797-808. [DOI:10.1111/bcp.14923] [PMID]

[18] Church MK, Kolkhir P, Metz M, Maurer M. The role and relevance of mast cells in urticaria. Immunological Reviews. 2018; 282(1):232-47. [DOI:10.1111/imr.12632] [PMID]

[19] Kuhn H, Kolkhir P, Babina M, Dull M, Frischbutter S, Fok JS, et al. Mas-related G protein-coupled receptor X2 and its activators in dermatologic allergies. The Journal of Allergy and Clinical Immunology. 2021; 147(2):456-69. [DOI:10.1016/j.jaci.2020.08.027] [PMID]

[20] Elieh-Ali-Komi D, Metz M, Kolkhir P, Kocaturk E, Scheffel J, Frischbutter S, et al. Chronic urticaria and the pathogenic role of mast cells. Allergology International. 2023; 72(3):359-68. [DOI:10.1016/j.alit.2023.05.003] [PMID]

[21] Yanase Y, Takahagi S, Ozawa K, Hide M. The role of coagulation and complement factors for mast cell activation in the pathogenesis of chronic spontaneous urticaria. Cells. 2021; 10(7):1759. [DOI:10.3390/cells10071759] [PMID]

[22] Kolkhir P, Altrichter S, Munoz M, Hawro T, Maurer M. New treatments for chronic urticaria. Annals of Allergy, Asthma & Immunology. 2020; 124(1):2-12. [DOI:10.1016/j.anai.2019.08.014] [PMID]

[23] Zoumakis E, Kalantaridou SN, Chrousos GP. The "brain-skin connection": Nerve growth factor-dependent pathways for stress-induced skin disorders. Journal of Molecular Medicine. 2007; 85(12):1347-9. [DOI:10.1007/s00109-007-0270-6] [PMID]

[24] Arnold IC, Dehzad N, Reuter S, Martin H, Becher B, Taube C, et al. Helicobacter pylori infection prevents allergic asthma in mouse models through the induction of regulatory T cells. The Journal of Clinical Investigation. 2011; 121(8):3088-93. [DOI:10.1172/JCI45041] [PMID]

[25] Ling Z, Li Z, Liu X, Cheng Y, Luo Y, Tong X, et al. Altered fecal microbiota composition associated with food allergy in infants. Applied and Environmental Microbiology. 2014; 80(8):2546-54. [DOI:10.1128/AEM.00003-14] [PMID]

[26] Hulshof L, Van't Land B, Sprikkelman AB, Garssen J. Role of microbial modulation in management of atopic dermatitis in children. Nutrients. 2017; 9(8):854. [DOI:10.3390/nu9080854] [PMID]

[27] Kristo M, Lugovic-Mihic L, Munoz M, Rupnik M, Mahnic A, Ozretic P, et al. Gut microbiome composition in patients with chronic urticaria: A review of current evidence and data. Life (Basel). 2023; 13(1):152. [DOI:10.3390/life13010152] [PMID]

[28] Zhu L, Jian X, Zhou B, Liu R, Munoz M, Sun W, et al. Gut microbiota facilitate chronic spontaneous urticaria. Nature Communications. 2024; 15(1):112. [DOI:10.1038/s41467-023-44373-x]

[29] Wang D, Guo S, He H, Gong L, Cui H. Gut microbiome and serum metabolome analyses identify unsaturated fatty acids and butanoate metabolism induced by gut microbiota in patients with chronic spontaneous urticaria. Frontiers in Cellular and Infection Microbiology. 2020; 10:24. [DOI:10.3389/fcimb.2020.00024] [PMID]

[30] Liu R, Peng C, Jing D, Xiao Y, Zhu W, Zhao S, et al. Biomarkers of gut microbiota in chronic spontaneous urticaria and symptomatic dermographism. Frontiers in Cellular and Infection Microbiology. 2021; 11:703126. [DOI:10.3389/fcimb.2021.703126] [PMID]

[31] Chang PV, Hao L, Offermanns S, Medzhitov R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proceedings of the National Academy of Sciences of the United States of America. 2014; 111(6):2247-52. [DOI:10.1073/pnas.1322269111] [PMID]

[32] Chiu CY, Chan YL, Tsai MH, Wang CJ, Chiang MH, Chiu CC. Gut microbial dysbiosis is associated with allergen-specific IgE responses in young children with airway allergies. The World Allergy Organization Journal. 2019; 12(3):100021. [DOI:10.1016/j.waojou.2019.100021] [PMID]

[33] Huang YJ, Nelson CE, Brodie EL, Desantis TZ, Baek MS, Liu J, et al. Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma. The Journal of Allergy and Clinical Immunology. 2011; 127(2):372-81. [DOI:10.1016/j.jaci.2010.10.048] [PMID]

[34] Nettis E, Di Leo E, Pastore A, Distaso M, Zaza I, Vacca M, et al. Probiotics and refractory chronic spontaneous urticaria. European Annals of Allergy and Clinical Immunology. 2016; 48(5):182-7. [PMID]

[35] Atefi N, Fallahpour M, Sharifi S, Ghassemi M, Roohaninasab M, Goodarzi A. Probiotic as an adjuvant therapy in chronic urticaria: a blinded randomized controlled clinical trial. European Annals of Allergy and Clinical Immunology. 2022; 54(3):123-30. [DOI:10.23822/EurAnnACI.1764-1489.200] [PMID]

[36] Liu R, Peng C, Jing D, Xiao Y, Zhu W, Zhao S, et al. Lachnospira is a signature of antihistamine efficacy in chronic spontaneous urticaria. Experimental Dermatology. 2022; 31(2):242-7. [DOI:10.1111/exd.14460] [PMID]

[37] Metz M, Krull C, Hawro T, Saluja R, Groffik A, Stanger C, et al. Substance P is upregulated in the serum of patients with chronic spontaneous urticaria. The Journal of Investigative Dermatology. 2014; 134(11):2833-6. [DOI:10.1038/jid.2014.226] [PMID]

[38] Almeida TA, Rojo J, Nieto PM, Pinto FM, Hernandez M, Martin JD, et al. Tachykinins and tachykinin receptors: structure and activity relationships. Current Medicinal Chemistry. 2004; 11(15):2045-81. [DOI:10.2174/0929867043364748] [PMID]

[39] Nishimori N, Toyoshima S, Sasaki-Sakamoto T, Hayama K, Terui T, Okayama Y. Serum level of hemokinin-1 is significantly lower in patients with chronic spontaneous urticaria than in healthy subjects. Allergology International. 2021; 70(4):480-8. [DOI:10.1016/j.alit.2021.05.002] [PMID]

[40] Basak PY, Erturan I, Yuksel O, Kazanoglu OO, Vural H. Evaluation of serum neuropeptide levels in patients with chronic urticaria. Indian Journal of Dermatology, Venereology and Leprology. 2014; 80(5):483. [DOI:10.4103/0378-6323.140345] [PMID]

[41] Zheng W, Wang J, Zhu W, Xu C, He S. Upregulated expression of substance P in basophils of the patients with chronic spontaneous urticaria: Induction of histamine release and basophil accumulation by substance P. Cell Biology and Toxicology. 2016; 32(3):217-28. [DOI:10.1007/s10565-016-9330-4] [PMID]

[42] Fadaee J, Khoshkhui M, Emadzadeh M, Hashemy SI, Farid Hosseini R, Jabbari Azad F, et al. Evaluation of serum substance P level in chronic urticaria and correlation with disease severity. Iranian Journal of Allergy, Asthma, and Immunology. 2020; 19(1):18-26. [DOI:10.18502/ijaai.v19i1.2414] [PMID]

[43] Boyvadoglu C, Ulusal H, Taysi S, Ozaydin-Yavuz G, Yavuz IH, Korkmaz P, et al. Effects of omalizumab on serum levels of substance P, Calcitonin Gene-Related Peptide, Neuropeptide Y, and interleukin-31 in patients with chronic spontaneous urticaria. Mediators of Inflammation. 2023; 2023:8087274. [DOI:10.1155/2023/8087274] [PMID]

[44] Acton D, Ren X, Di Costanzo S, Dalet A, Bourane S, Bertocchi I, et al. Spinal neuropeptide Y1 receptor-expressing neurons form an essential excitatory pathway for mechanical itch. Cell Reports. 2019; 28(3):625-39 e6. [DOI:10.1016/j.celrep.2019.06.033] [PMID]

[45] Basak PY, Vural H, Kazanoglu OO, Erturan I, Buyukbayram HI. Effects of loratadine and cetirizine on serum levels of neuropeptides in patients with chronic urticaria. International Journal of Dermatology. 2014; 53(12):1526-30. [DOI:10.1111/ijd.12590] [PMID]

[46] Borici-Mazi R, Kouridakis S, Kontou-Fili K. Cutaneous responses to substance P and calcitonin gene-related peptide in chronic urticaria: The effect of cetirizine and dimethindene. Allergy. 1999; 54(1):46-56. [DOI:10.1034/j.1398-9995.1999.00726.x] [PMID]

[47] Kay AB, Ying S, Ardelean E, Mlynek A, Kita H, Clark P, et al. Calcitonin gene-related peptide and vascular endothelial growth factor are expressed in lesional but not uninvolved skin in chronic spontaneous urticaria. Clinical and Experimental Allergy. 2014; 44(8):1053-60. [DOI:10.1111/cea.12348] [PMID]

[48] Zhang Y, Zhang H, Jiang B, Tong X, Yan S, Lu J. Current views on neuropeptides in atopic dermatitis. Experimental Dermatology. 2021; 30(11):1588-97. [DOI:10.1111/exd.14382] [PMID]

[49] Ayasse MT, Buddenkotte J, Alam M, Steinhoff M. Role of neuroimmune circuits and pruritus in psoriasis. Experimental Dermatology. 2020; 29(4):414-26. [DOI:10.1111/exd.14071] [PMID]

[50] Schulte-Herbrüggen O, Fölster-Holst R, von Elstermann M, Augustin M, Hellweg R. Clinical relevance of nerve growth factor serum levels in patients with atopic dermatitis and psoriasis. International Archives of Allergy and Immunology. 2007; 144(3):211-6. [DOI:10.1159/000103994] [PMID]

[51] Choi JE, Di Nardo A. Skin neurogenic inflammation. Seminars in Immunopathology. 2018; 40(3):249-59. [DOI:10.1007/s00281-018-0675-z] [PMID]

[52] Arck PC, Slominski A, Theoharides TC, Peters EM, Paus R. Neuroimmunology of stress: Skin takes center stage. The Journal of Investigative Dermatology. 2006; 126(8):1697-704. [DOI:10.1038/sj.jid.5700104] [PMID]

[53] Elcin A, Ayla G, Tuba Saadet Deveci B, Ozlem G, Murat O, Ahmet Selim B, et al. Stressful life events, psychiatric comorbidities and serum neuromediator levels in patients with chronic spontaneous urticaria treated with omalizumab. Allergologia et Immunopathologia. 2024; 52(3):1-7. [DOI:10.15586/aei.v52i3.1015] [PMID]

[54] Joachim RA, Kuhlmei A, Dinh QT, Handjiski B, Fischer T, Peters EM, et al. Neuronal plasticity of the "brain-skin connection": Stress-triggered up-regulation of neuropeptides in dorsal root ganglia and skin via nerve growth factor-dependent pathways. Journal of Molecular Medicine. 2007; 85(12):1369-78. [DOI:10.1007/s00109-007-0236-8] [PMID]

[55] Babina M, Guhl S, Artuc M, Zuberbier T. Allergic FcepsilonRI- and pseudo-allergic MRGPRX2-triggered mast cell activation routes are independent and inversely regulated by SCF. Allergy. 2018; 73(1):256-60. [DOI:10.1111/all.13301] [PMID]

[56] Stander S, Luger TA. NK-1 Antagonists and itch. Handbook of Experimental Pharmacology. 2015; 226:237-55. [DOI:10.1007/978-3-662-44605-8_14] [PMID]

[57] Wallengren J. Substance P antagonist inhibits immediate and delayed type cutaneous hypersensitivity reactions. The British Journal of Dermatology. 1991; 124(4):324-8. [DOI:10.1111/j.1365-2133.1991.tb00591.x] [PMID]

[58] Kocaturk E, Maurer M, Metz M, Grattan C. Looking forward to new targeted treatments for chronic spontaneous urticaria. Clinical and Translational Allergy. 2017; 7:1. [DOI:10.1186/s13601-016-0139-2]