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# Beyond the itch: the complex interplay of immune, neurological, and psychological factors in chronic urticaria

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## Abstract

Chronic urticaria (CU) arises from a multifaceted interplay of immunological, neurological, and psychological components. Immune dysregulation, mediated through both immunoglobulin E (IgE)-dependent and IgE-independent pathways, plays a pivotal role in CU pathogenesis, involving key effector cells such as mast cells (MCs), basophils, and eosinophils. This dysregulation culminates in the release of histamine, prostaglandins, and other mediators, which precipitate pruritus. The chronicity of the disease leads to sustained pruritic symptoms, contributing to both central and peripheral sensitization. The excitation of the itch circuit is augmented, leading to the release of neurotransmitters and neuropeptides, which subsequently interact with immune cells. Psychological factors such as depression, anxiety, and stress exacerbate CU symptoms and diminish quality of life. These factors disrupt the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS). Furthermore, the act of scratching activates the reward circuit, resulting in the manifestation of the itch-scratching cycle. Current treatments, such as antihistamines, omalizumab, and cyclosporine, demonstrate variable efficacy and are often associated with adverse effects. A holistic approach addressing both psychological and physiological aspects is advocated. This review highlights the critical importance of understanding neuroimmune interactions and the influence of psychosomatic factors in CU. It aims to enhance diagnostic and therapeutic strategies by integrating psychological, neurological, and immunological perspectives.

**Keywords** Chronic urticaria, Neuroimmunity, Depression, Anxiety, Stress, Itch, Reward circuit

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## Background

CU is a multifactorial skin disorder. The overall lifetime prevalence of CU is 4.4% [1], with a higher prevalence among women, particularly during their youth and middle age [2]. Characterized by recurrent wheals and angioedema lasting for six weeks or more, CU significantly impacts various physiological systems, including the integumentary, cardiovascular, respiratory, gastrointestinal, central nervous, and musculoskeletal systems [3, 4]. This multi-system involvement highlights the complexity of the disease. Up to 85.9% of patients report experiencing CU symptoms during work, with more than half noting a considerable reduction in their productivity due to the condition [5].

CU is typically classified into two main types. Chronic inducible urticaria (CIndU) is triggered by identifiable external factors such as medication, physical stimuli, or stress, while chronic spontaneous urticaria (CSU) lacks a clear external trigger [6, 7]. In patients with CSU, stress may also exacerbate disease activity [8]. CU is closely associated with immune dysregulation via both IgE-dependent and IgE-independent pathways [9–11]. The release of histamine and other inflammatory mediators results in intense itching and swelling. Although second-generation antihistamines, omalizumab, and cyclosporine are standard treatments with an efficacy of 60–80%, they are not universally effective and are often accompanied by side effects such as headaches and drowsiness [12–15].

In addition, CU is heavily influenced by neurological and psychological factors [16]. The interaction between the immune system, nerve system, and psychological states form a complex network of neuroimmune interactions. About 25% of people with skin diseases also exhibit depression, anxiety, or somatoform reactions [17]. Patients with CU often experience psychiatric disorders [18]. Psychological stress is known to exacerbate CU symptoms, creating a vicious cycle where itching leads to increased stress, which, in turn, worsens the itching. This cycle significantly lowers the quality of life and complicates treatment [19–21]. Sleep disturbances and heightened anxiety have been shown to correlate with increased disease activity in CU [22], further emphasizing the role of psychological comorbidities in the progression of disease.

Despite significant progress in elucidating the mechanisms underlying CU, our comprehension of the intricate interactions among the immune, neurological, and psychological systems that sustain and exacerbate this condition remains incomplete. Existing animal models offer valuable insights, but they inadequately represent the complexity of CU in humans. The disparities in skin architecture, immune responses, and neuroimmune signaling between humans and animal models further constrain the reliability of these preclinical systems. Consequently, the translation of preclinical findings into clinical practice continues to pose significant challenges, potentially impeding the advancement of effective therapeutic interventions. This highlights the pressing necessity for the development of more sophisticated models that incorporate neuroimmune and psychological factors, thereby more accurately representing the complexities inherent in human CU pathology. Furthermore, in the basis of scrutinizing psychological elements on this crosstalk, a comprehensive approach to diagnosis and treatment is also advocated.

## Immune cell involvement and animal models about CU

### Activation and recruitment of immune cells

The etiology of CSU and CIndU remains incompletely understood, with distinct immune cell mechanisms implicated in each condition. CIndU comprises several subtypes, including cold urticaria, heat urticaria, delayed pressure urticaria, symptomatic dermographism, solar urticaria, vibratory angioedema, cholinergic urticaria, contact urticaria, and aquagenic urticaria. Current evidence suggests that CSU involves the dysregulation of various immune cells, including MCs, basophils, eosinophils, T cells, B cells, and neutrophils, whereas CIndU is primarily associated with aberrant activation of MCs and basophils. Investigating the activation and regulation of these immune cells in CU is of importance, as depicted in Figs. 1 and 2.

#### *MCs*

The activation of MCs is the result from antigen binding to IgE antibodies and cross-linking of the high-affinity IgE receptor (FcεRI) [23]. 25% patients had levels of anti-FcεRI IgE in CSU [24]. MAS-related G protein-coupled receptor X2 (MRGPRX2) exhibits a high level of expression in cutaneous MCs. Its activation releases degranulation products and pro-inflammatory mediators, promoting multicellular signaling and initiating itch signals in sensory neurons [25]. It is also involved in IgE-independent pathways in CU [26]. Subsequently, the manifestation of urticaria is observed [27].

Three factors triggering MC activation in CSU are receptor stimulation, receptor upregulation, and intracellular dysregulation from overexpression of spleen tyrosine kinase or activation of the inhibitory Src homology 2 domain-containing inositol phosphatase-related pathway [28]. Th2 inflammation, B cell autoantibodies, basophil-released histamine, and eosinophil or monocyte initiation of the extrinsic coagulation pathway strongly influence MC regulation in CSU [29]. In CSU, histamine-induced expression of tissue factor (TF) on endothelial cells initiates the extrinsic coagulation pathway, leading

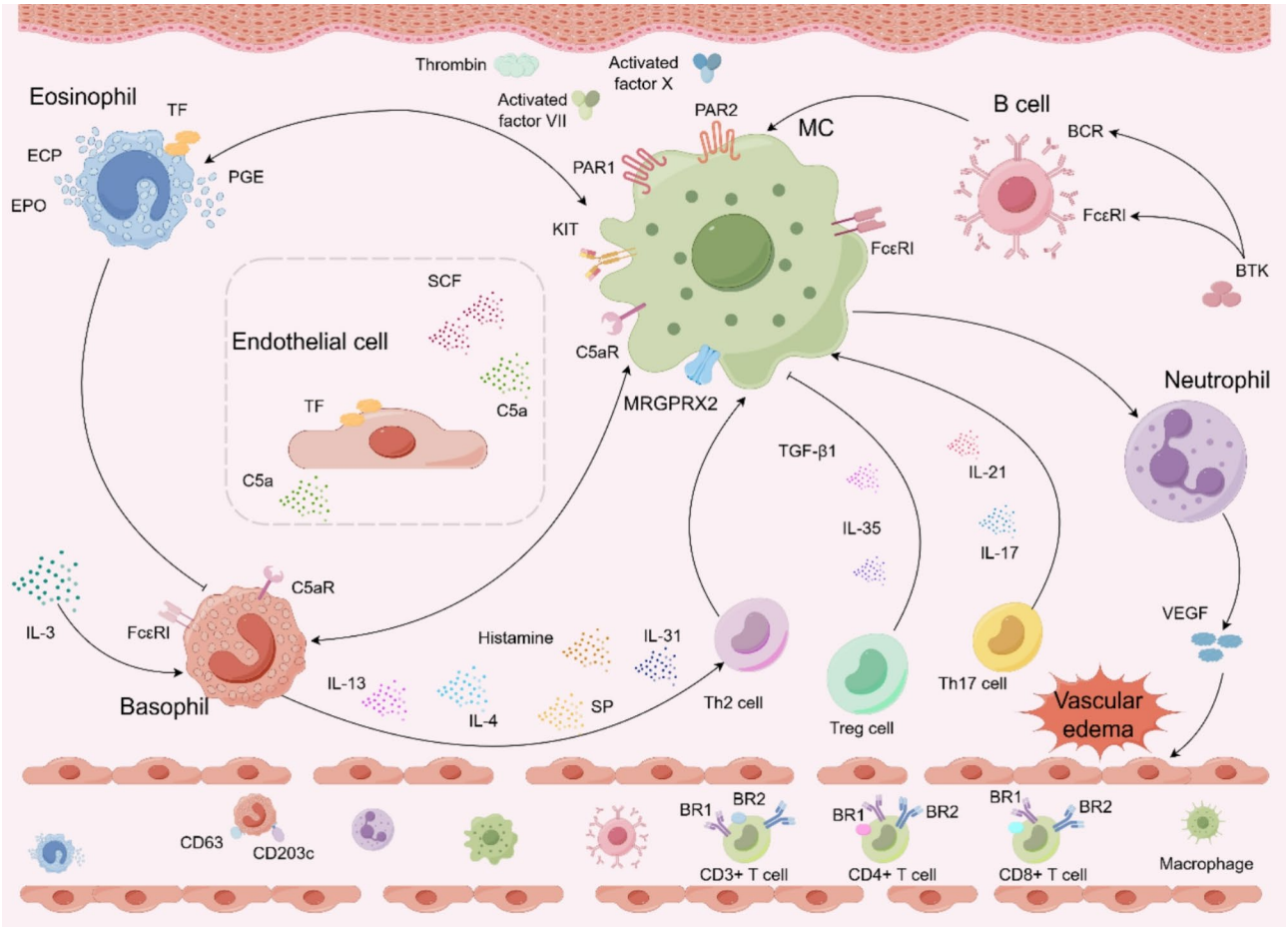


**Fig. 1** Aberrant activation and interaction of immune cells in CSU. The figure was created using Figdraw (ID: WPASA0bd00). MCs are activated, leading to the release of inflammatory mediators that initiate pruritus. Basophils contribute to pruritus via Th2 responses and the release of pruritic mediators. Eosinophils, linked to severe urticaria, work to suppress basophils. Additionally, neutrophils, T cells and other immune cells, including Th17 cells and B cells, are implicated in the pathophysiology of CSU. The condition is characterized by elevated inflammatory markers and dysregulation of immune cells, with M2 macrophages fostering a Th2-dominant environment

to the production of complement 5a (C5a), an anaphylatoxin that subsequently activates both basophils and MCs via the C5a receptor (C5aR) [30]. Additionally, in CSU, upregulated expression of stem-cell factor (SCF) in the skin promotes MC activation through its interaction with the stem-cell factor receptor (KIT) [31]. Certain elements of the coagulation cascade, including thrombin and the complex of activated factor VII, activated factor X, and tissue factor, have the capacity to induce MC degranulation through the activation of protease-activated receptor 1 (PAR1) and protease-activated receptor 2 (PAR2), respectively, in CSU [32–34].

CIndU involves MC-triggered wheals in reaction to specific stimuli [35, 36]. Histamine release from dermal MCs is central to CIndU symptoms [37]. In cold urticaria, cold-induced autoallergens lead to IgE production, causing MC degranulation and proinflammatory mediator release [38]. And the activation of MCs via the phosphoinositide 3-kinase (PI3K)/ protein kinase B (Akt)/ nuclear factor kappa-B (NF-κB) pathway is crucial in immunologic contact urticaria [39].

### *Basophils*

Basophils participate in the Th2 immune response and engage in interactions with other skin cells, secreting a range of pruritic mediators such as histamine, interleukin-4 (IL-4), interleukin-13 (IL-13), interleukin-31 (IL-31), and substance P (SP) [40, 41]. Activated basophils exhibit heightened sensitivity to interleukin-3 (IL-3) stimulation, suggesting that deficiencies in signal transduction pathways may be rectified in patients with CU following stimulation of IgE crosslinking [42].

During CSU activity, the expression levels of IgE receptor signaling molecules in blood basophils change, accompanied by altered degranulation functions [43]. The basophil activation phenotype is associated with a longer disease duration in CSU [44–46]. Decreased peripheral basophil counts may be due to the recruitment

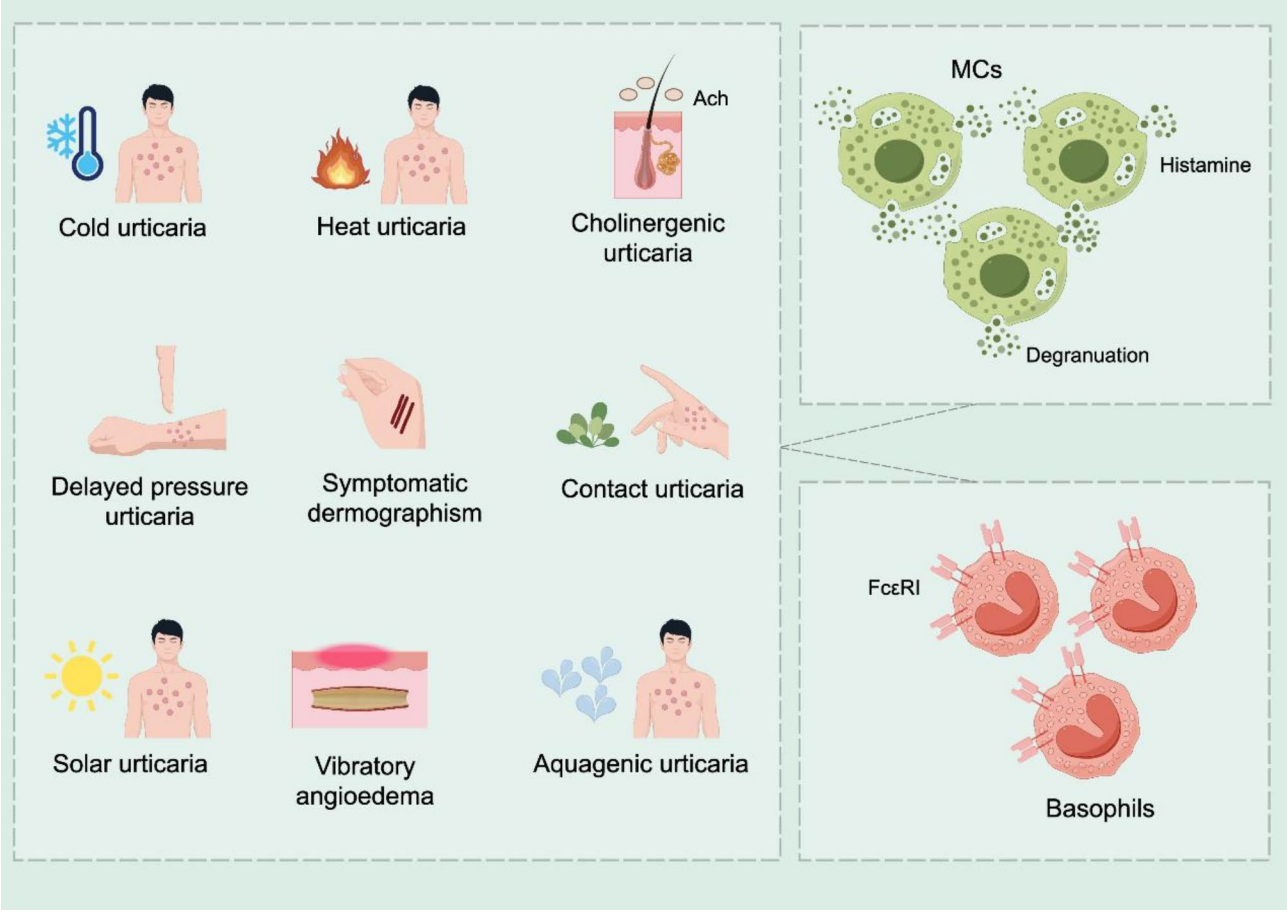


**Fig. 2** Abnormal activation of immune cells in CIndU. The figure was created using Figdraw (ID: WUUTA43559). MC degranulation and highly active FcεRI on the surface of basophils are involved in the development of CIndU

of basophils to the site of skin lesions in CSU [47]. The increased CD63 in CSU patients is related to allergen sensitivity, serum autoreactivity, and basophilic reactivity [48]. Serum basophilic CD203c upregulation and positive autologous serum skin tests were significantly correlated with basophilic histamine release in CSU [49]. Additionly, basophils in the bloodstream of CSU patients have impaired IgE-mediated pathways but retain heightened responsiveness to C5a and histamine [30].

In CIndU, they have shown slight activation in peripheral blood but no abnormalities in responsiveness [50]. The median expression of FcεRI, normalized per density, in blood basophils has demonstrated a significant increase [51].

#### *Eosinophils*

Eosinophils are a type of granulocyte containing eosinophilic granules. They inhibit basophil activity by releasing prostaglandin E (PGE) and phagocytosing granules expelled by basophils, as well as releasing histaminase to destroy active substances released by basophils. They also release eosinophil peroxidase (EPO) and eosinophil cationic protein (ECP), and sustained exposure to these proteins may trigger an autoimmune response [52]. It is worth noting that eosinophilic inflammatory infiltrates indicate high clinical activity, which means more severe and vigorous clinical manifestations of CU [53, 54]. Besides that, in patients with metabolic syndrome, urticaria activity scores and serum levels of ECP, tumor necrosis factor-α (TNF-α), and complement were higher [55]. In CSU, vascular endothelial cells and eosinophils may act as TF-expressing cells, thereby activating the exogenous clotting pathways [56]. Blood eosinophilia is associated with positive autoserum skin tests and basophilic histamine release tests, low total IgE, and high levels of C-reactive protein and Immunoglobulin G (IgG)-antithyroid peroxidase in CSU [57].

#### *Neutrophils and other immune cells*

In delayed IgE-mediated hypersensitivity reactions, neutrophils are suggested to function as antigen-presenting cells and are linked to the upregulation of calcitonin gene-related peptide (CGRP) and vascular endothelial growth factor (VEGF) in CSU [58]. It's hypothesized that

**Table 1** The immunity-related animal models of CSU

| Animals | Type | Drugs | Methods | Manifestations | References |
|---|---|---|---|---|---|
| Male C57BL/6 mice | CSU | OVA IgE antiserum | The mice were intradermally injected with 0.1 mL of normal saline solution containing OVA IgE antiserum (1:1 ratio). After sensitization, the mice were subjected to an antigen challenge by injecting 0.5% Evans blue solution (containing 30 mg OVA) into the tail vein. | Itch, bright red or pale wheals of varying sizes | [65] |
| Male C57BL/6 mice | CSU | OVA | OVA (20 μg/ml) was injected intraperitoneally into the mice. | Paw swelling | [66] |
| Sprague Dawley rats | CSU | OVA | Rats received an intraperitoneal injection of 1 mL OVA (1 mg) suspension, followed by a second injection with aluminum hydroxide after 5 days. | Increased frequency of scratching behavior and reduced scratching duration | [67] |
| Kunming mice | CAU | OVA | Each mouse received an intraplantar injection of 0.05 mL 5% OVA in saline (total 0.1 mL) and an intraperitoneal injection of pertussis vaccine ($4 \times 10^9$ U). | Increased frequency of scratching behavior and reduced scratching duration | [68] |
| Kunming mice | CSU | Histamine | The mice were subcutaneously injected with 0.1 mL of 10 mg/mL histamine into the abdomen. | Increased frequency of scratching behavior and reduced scratching duration | [60] |
| Kunming mice | CSU | Histamine | The mice were subcutaneously injected with 0.1 mL of histamine solution (10 mg/mL) into the back. | Wheals, rashes | [69] |

**Table 2** The immunity-related animal models of CIndU

| Animals | Type | Drugs | Methods | Manifestations | References |
|---|---|---|---|---|---|
| Female BALB/c mice | Contact urticaria | TMA | Mice were sensitized by applying 100 μL of TMA (500 mg/mL) in acetone/olive oil (4:1, v/v) to the shaved hind flank. Secondary sensitizations with 50 μL of TMA (250 mg/mL) were performed on days 7 and 10. On day 13, contact urticaria was induced by applying 25 μL of TMA (100 mg/mL) to the ears. | Ear swelling, itching and lesions on the skin | [70] |
| Female Balb/c mice | Contact urticaria | TMA | A approximately 4 $cm^2$ area on the trunk of animals was shaved and tape-stripped three times before applying 100 μL of 500 mg/mL TMA topically. Allergy induction was repeated at the same site with 50 μL of 250 mg/mL TMA after 7 days. | Ear swelling | [71] |
| BALB/c mice | ICU | TMA | ICU mice were depilated (2 cm × 3 cm) and treated with 100 μL TMA (500 mg/mL), followed by 50 μL TMA (250 mg/mL) daily for 7 days. On day 6, 25 μL TMA (100 mg/mL) was applied to both ears to induce ICU. | Wheals, scratching behavior, swelling | [72] |
| Male C57BL/6 mice and BALB/c mice | Contact urticaria | DNP-IgE monoclonal antibody combined with DNFB | Model mice were injected with 0.2 ml of saline-diluted anti-DNP IgE antibody. After 24 h, 0.2% DNFB (Olive oil: Acetone = 1:3) was applied to both ears and the back of the mice, with the normal group receiving solvent. | Scratching behavior, ear swelling, and wheal | [39] |

B-cell receptor (BCR) signaling plays a vital role in CSU by fostering the generation of autoreactive B cells and the production of autoantibodies. And the proportion of immature $CD4^+$ T cells is lower [59]. Mice with CSU exhibited elevated $CD8^+$ expression and an increased $CD4^+/CD8^+$ ratio [60]. Th17 cells and cytokines such as interleukin-17 (IL-17) and interleukin-21 (IL-21), are associated with more severe CSU symptoms, while a decrease in regulatory T (Treg) cells and their cytokines, including transforming growth factor-beta 1 (TGF-β1) and interleukin-35 (IL-35), has also been observed [61]. Furthermore, a significant upregulation of bradykinin receptor 1 (BR1) expression has been observed in lymphocyte subsets, including $CD3^+$ T cells, $CD4^+$ T cells, and $CD8^+$ T cells, in patients with CSU [62]. Bruton tyrosine kinase (BTK) is crucial to both FcεRI and BCR signaling pathways [63]. The predominant M2 type macrophage population in CSU skin lesions contributes to the maintenance of a Th2-mediated inflammatory environment, thus fostering the development of CSU [64].

### Immunity-related animal models of CU might apply or differ in human conditions

The current CU models are summarized in Tables 1 and 2. Ovalbumin (OVA)-induced CSU models are widely used. Some are designed to mimic key CSU features like wheal formation, MC degranulation, and inflammatory cytokine release. CIndU models are still limited, with reports primarily focusing on contact urticaria models

induced by trimellitic anhydride (TMA), while models for other subtypes remain scarce.

#### *Animal model of CSU*

A CSU mouse model, created through intradermal OVA IgE antiserum injection, replicates CSU symptoms like itching and wheals, confirmed by hematoxylin-eosin staining [65]. Another model uses intraperitoneal OVA and aluminum hydroxide to induce an IgE response, causing wheals and pruritus similar to human CSU [66]. However, not all models exhibit wheals, which may limit their broader application. For instance, Janus kinase (JAK)/ signal transducer and activator of transcription (STAT) pathway gene-silencing reduces inflammation but lacks wheal formation, limiting its relevance [67]. The chronic autoimmune urticaria (CAU) mouse model, a CSU subset, uses OVA sensitization and anti-OVA antiserum to mimic chronic inflammation and MC activation [68].

A common model uses subcutaneous histamine injection to trigger wheal-and-flare reactions, simulating MC degranulation and increased vascular permeability [69]. It also shows eosinophil infiltration, itching, and the roles of interleukin-9 (IL-9) and interleukin-10 (IL-10) through the JAK/STAT pathway, mainly emphasizing cytokine regulation [60]. Since wheal formation is crucial for diagnosing CSU, models lacking transient edema as a main feature should be carefully evaluated for CSU research.

#### *Animal model of CIndU*

Applying TMA to mice skin induces an IgE response, leading to MC degranulation and ear swelling, mimicking contact urticaria [70, 71]. Immunologic contact urticaria (ICU) mice develop transient wheals on their skin [72]. The ICU mouse model is also created by injecting 2,4-Dinitrophenol (DNP)-IgE antibody and applying 2,4-dinitrofluorobenzene (DNFB) to trigger an IgE-mediated allergic reaction, activating MCs and causing wheals and itching [39]. These reports only mention information about wheals in about half of the cases. Due to the limited number of reports currently available, it is difficult to assess whether this model can effectively reflect clinical manifestations.

## Neurological mechanisms and sensitization

### Association between neuronal excitation and immune cell in CU

Recent studies have increasingly demonstrated that CU, similar to other type 2 inflammatory skin diseases like atopic dermatitis, involves an interaction between immune cells and sensory neurons that worsens the condition. In CU, immune cells including MCs, eosinophils, and T/B lymphocytes release cytokines such as IL-4, IL-13, interleukin-33 (IL-33), and IL-31, which regulate chronic itch by acting on sensory neurons or modifying their sensitivity to pruritogens [73, 74]. MCs release IL-33 upon activation, leading to the amplification of histamine-induced itch through an IL-13-dependent mechanism in CU [75]. CU may also involve central sensitization. Chronic itching and skin inflammation in CU can alter the spinal cord and brain, increasing excitability and weakening inhibitory circuits, thus greatly intensifying itch perception.

#### *Central sensitization and peripheral sensitization*

Wheals and/or angioedema represent cutaneous responses elicited by inflammatory mediators, whereas pruritus is induced when these mediators interact with sensory nerve endings. Itch signals are conveyed by unmyelinated C-fibers to the dorsal root ganglia, subsequently relayed to the dorsal horn of the spinal cord, and ultimately transmitted to the brain [76]. Persistent itching triggers alterations in the spinal cord and brain. Specifically, within the spinal cord, the constant bombardment of itching stimuli can heighten the excitability of dorsal horn neuron [77, 78]. This encompasses increased activity within itch-inducing neural pathways, impairment of inhibitory circuits within the spinal cord, and diminished effectiveness of inhibitory pathways originating from higher brain regions [79, 80]. The phenomenon known as central sensitization significantly amplifies and extends the responses to pruritic stimuli. Additionally, pruritic stimuli can sensitize peripheral nerve fibers, particularly the C-fibers responsible for transmitting itch sensations, a process termed peripheral sensitization. Sensory nerve endings exhibit increased responsiveness to pruritogenic mediators such as histamine and proteases, leading to enhanced neuronal excitability and intensified local inflammation [81–83]. This, in turn, amplifies and prolongs the sensation of itch. The worsening of itch leads to increased scratching behavior, resulting in mechanical damage to the skin. The degranulation of immune cells and the subsequent release of inflammatory mediators are facilitated, leading to capillary dilation and increased permeability. These changes exacerbate the swelling associated with wheals and angioedema.

#### *Itch transmission and modulation in the central nervous system*

The substances released by immune cells and sensory nerve endings are the primary contributors to the chemical itch in CU, while scratching further induces mechanical itching. In chemical pruritus, keratinocytes communicate directly with sensory neurons through synaptic-like contacts via soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-dependent vesicle release mechanisms, thereby activating sensory neurons [84]. Activation of D1/D5 dopamine

receptors and metabotropic glutamate receptor 5 (mGluR5) in the spinal cord can induce non-Hebbian long-term potentiation at sensory synapses without the strict requirement of synchronized presynaptic and postsynaptic activity, amplifying pain and itch signals transmitted to the brain [85]. Mas-related G protein-coupled receptor A3 (MrgprA3)$^+$ neurons are a specialized subpopulation of sensory neurons located in the dorsal root ganglia and trigeminal ganglia by responding to various pruritogens, including both histamine-dependent and histamine-independent stimuli. In chronic itch conditions, MrgprA3$^+$ neurons become more sensitive and excitable, with upregulated ion channels and receptors driving the persistence and severity of the itch [86]. Gastrin-releasing peptide (GRP) neurons receive direct input from MrgprA3$^+$ pruritoceptors [87]. Gastrin-releasing peptide receptor (GRPR)-expressing neurons in the spinal cord form disynaptic connections with glutamatergic spinal projection neurons, mediating itch [88]. Spinal GRPR$^+$ neurons receive inhibitory synaptic inputs from local galanin + gamma-aminobutyric acid (GABA)ergic neurons and long-range neurons from the rostral ventromedial medulla (RVM), which together regulate the transmission of itch signals and dynamically modulate itch perception at the spinal level [89]. Microglia promote chronic itch by producing interleukin-1β (IL-1β) through the activation of the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome and subsequently activating GRPR$^+$ neurons via the type 1 IL-1 receptor (IL-1R1) [90]. Hypothalamic orexin neurons alleviate pain and exacerbate itch by activating periaqueductal gay (PAG) neurons through orexin-dependent and independent pathways, respectively [91]. Activating cannabinoid receptor type 1 (CB1) expressed on glutamatergic neurons and downregulating CB1 on GABAergic neurons in the ventrolateral PAG to alleviate chronic itch leads to the release of 5-hydroxytryptamine (5-HT) in the rostral ventromedial medulla and a reduction in GRPR signaling in the spinal cord [92]. Locus coeruleus (LC) noradrenergic (NAergic) neurons facilitate inhibitory synaptic inputs through activation of α1A-adrenergic receptors (α1AAR) on inhibitory interneurons that project onto GRPR$^+$ neurons [93].

In addition to chemical pruritus, CU also involves mechanical pruritus. In the spinal cord, urocortin 3 (Ucn3)$^+$ excitatory interneurons specifically mediate and regulate mechanical itch by receiving inputs from Toll-like receptor 5$^+$ Aβ low-threshold mechanoreceptors (LTMRs). These Ucn3 + neurons are modulated by feed-forward inhibition from neuropeptide Y (NPY)$^+$ inhibitory interneurons [94]. The inhibitory effect of NPY$^+$ interneurons may involve the activation of the neuropeptide Y1 receptor (NPY1R) [95]. In chronic itch, the down-regulation of Nav1.6 channels in NPY$^+$ neurons reduces inhibition of Ucn3$^+$ neurons, leading to excessive transmission of mechanical itch signals, while the excitability of NPY-expressing spinal neurons is significantly diminished during persistent itch [96]. Ucn3$^+$ neurons transmit mechanical itch signals to sensory brain regions, particularly the parabrachial nucleus (PBN), via spinoparabrachial projection neurons that express calcitonin receptor like receptor (Calcrl), making synapses with PBN neurons which express forkhead box protein P2 (FoxP2) [97]. The transmission of itch signal from skin to brain is shown in Fig. 3.

#### *Neurons interact bidirectionally with immune cells in chronic itch*

The skin functions as both a physical barrier and an active player in neuro-immunological interactions. Neuropeptides and neurotransmitters from neurons regulate immune cells, which in turn activate neurons through inflammatory mediators [98, 99]. Sensory neurons, including those expressing transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1), participate in a bidirectional interaction with immune cells through the expression of immune receptors and the release of neuropeptides [100]. SP, released by sensory nerves in the skin, causes wheals and itching by promoting vasodilation, increasing vascular permeability, transmitting itch signals, and triggering MCs to release histamine and prostaglandin D2 (PGD2) [101]. Activation of MRGPRX2 by the neuropeptide SP is implicated in CU [102, 103]. Upon binding to the H1 receptor (H1R), histamine activates the TRPV1 channel on sensory neurons, resulting in nerve discharge signals that produce the sensation of itching. PGD2, through activation of the chemoattractant receptor-homologous molecule expressed on Th2 cells receptor (CRTH2R), directly influences sensory neurons, augmenting their excitability and consequently enhancing pain sensitivity. They forms a feedback loop, further amplifying neurogenic inflammation and itch in chronic skin conditions [104]. In CSU, there is a significant increase in circulating levels of SP related to the severity of the disease, activating MCs and stimulating the degranulation of basophilic granulocytes [105]. These effects are mainly achieved through the neurokinin-1 receptor (NK1R). However, there are also reports that SP values were not correlated with the severity of urticaria or angioedema [106]. In addition, sensory nerves release CGRP, contributing to vasodilation and inflammation. Lesional skin in CSU contained significantly more CGRP$^+$ cells than non-lesional skin [107]. Although the neuroimmune mechanisms in CU require further exploration, the interaction between immune cells and the nervous system has been demonstrated in certain dermatosis models. interleukin-27 (IL-27) promotes neuroimmune interactions and exacerbates

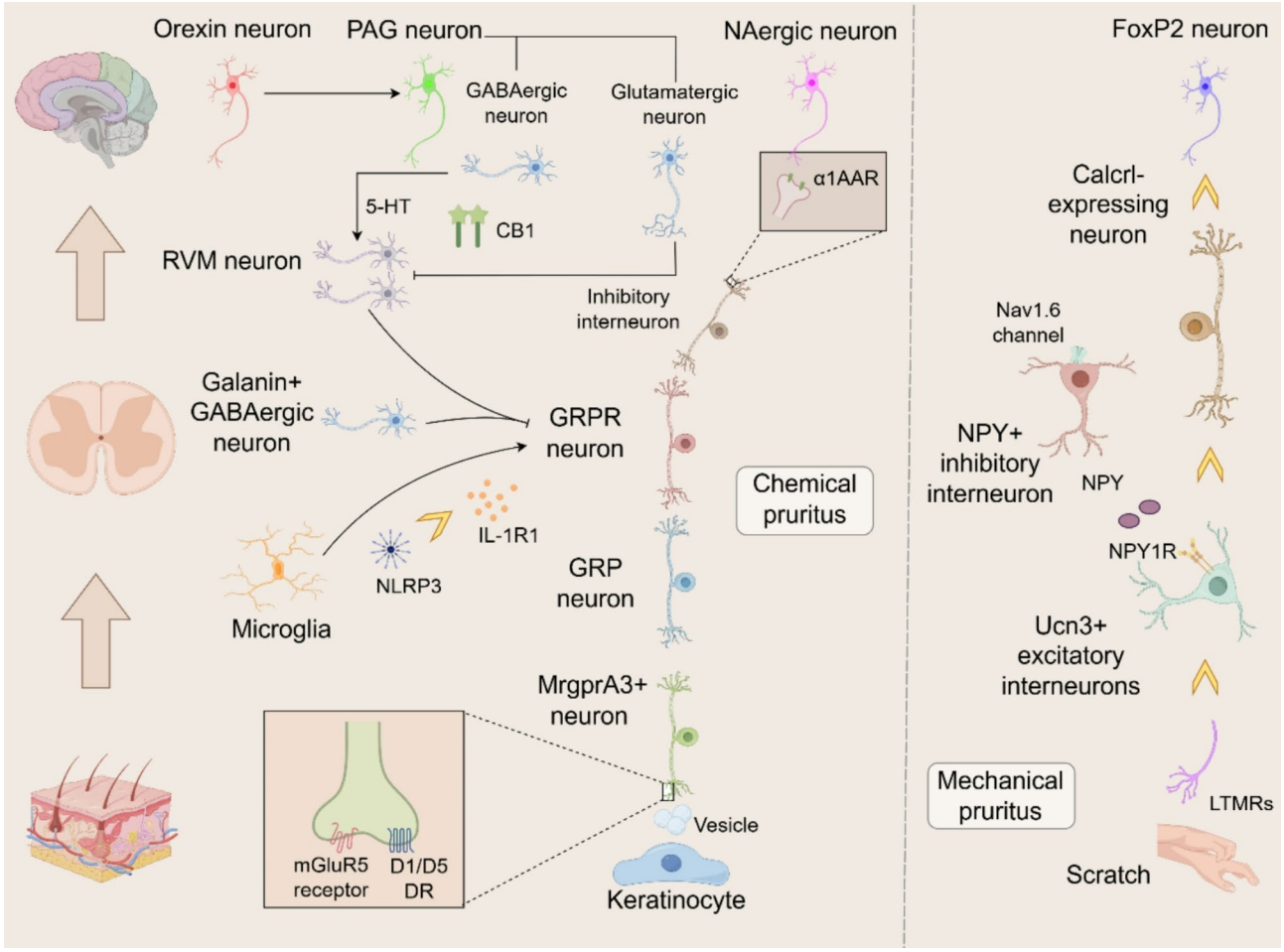


**Fig. 3** Itch Transmission and Modulation in the Nervous System from Peripheral to Central Pathways. The figure was created using Figdraw (ID: PUSUA074f4). In chronic itch, keratinocytes communicate directly with sensory neurons through SNARE-dependent vesicle release, triggering itch signals. MrgprA3$^+$ neurons respond to pruritogens, while GRPR$^+$ neurons mediate itch via disynaptic connections. Ucn3$^+$ neurons specifically transmit mechanical itch signals from TLR5$^+$ Aβ mechanoreceptors to the PBN, regulated by NPY$^+$ inhibitory neurons. Chronic itch sensitization involves reduced inhibition of Ucn3$^+$ neurons due to downregulated Nav1.6 channels in NPY$^+$ neurons, leading to excessive itch signal transmission to sensory brain regions

chronic itch by increasing the expression of bone marrow stromal antigen 2 (BST2) in sensory neurons and keratinocytes and upregulating the activity of PAR2 [108]. Eosinophils promote increased neurite branching in sensory neurons by releasing non- nerve growth factor (NGF)-dependent factors, thereby enhancing nerve density [109]. Basophils mediate acute itch by releasing leukotriene C4 (LTC4), which activates cysteinyl leukotriene receptor 2 (CysLTR2) on sensory neurons, triggering the itch sensation via TRPV1 and TRPA1 calcium channels [110, 111]. Additionally, basophils upregulate tetrahydrobiopterin (BH4), enhancing the release of itch mediators like histamine and serotonin from MCs, while directly activating TRPA1 channels, further intensifying the sensation of itch [112]. These communications are indicated in Fig. 4.

### Neuro-immuity-related animal models of CU might apply or differ in human conditions

Injecting SP subcutaneously into mice induces MC degranulation, histamine release, and an inflammatory response, effectively simulating CU symptoms in humans [113]. The strength lies in replicating key CU processes, especially MC-mediated inflammation, while also revealing the connection between SP and the Src kinase signaling pathway. It further demonstrated the potential of paeonol, a natural compound, in inhibiting MC activation, offering clinical application potential. However, the model focuses heavily on the MRGPRX2 pathway, overlooking other immune mechanisms that may contribute to CU. Additionally, it induces symptoms like wheals and itching through SP-induced MC degranulation in Balb/c mice [114]. Another similar model mimics CSU by triggering both IgE-mediated and pseudo-allergic reactions, leading to MC degranulation and inflammatory

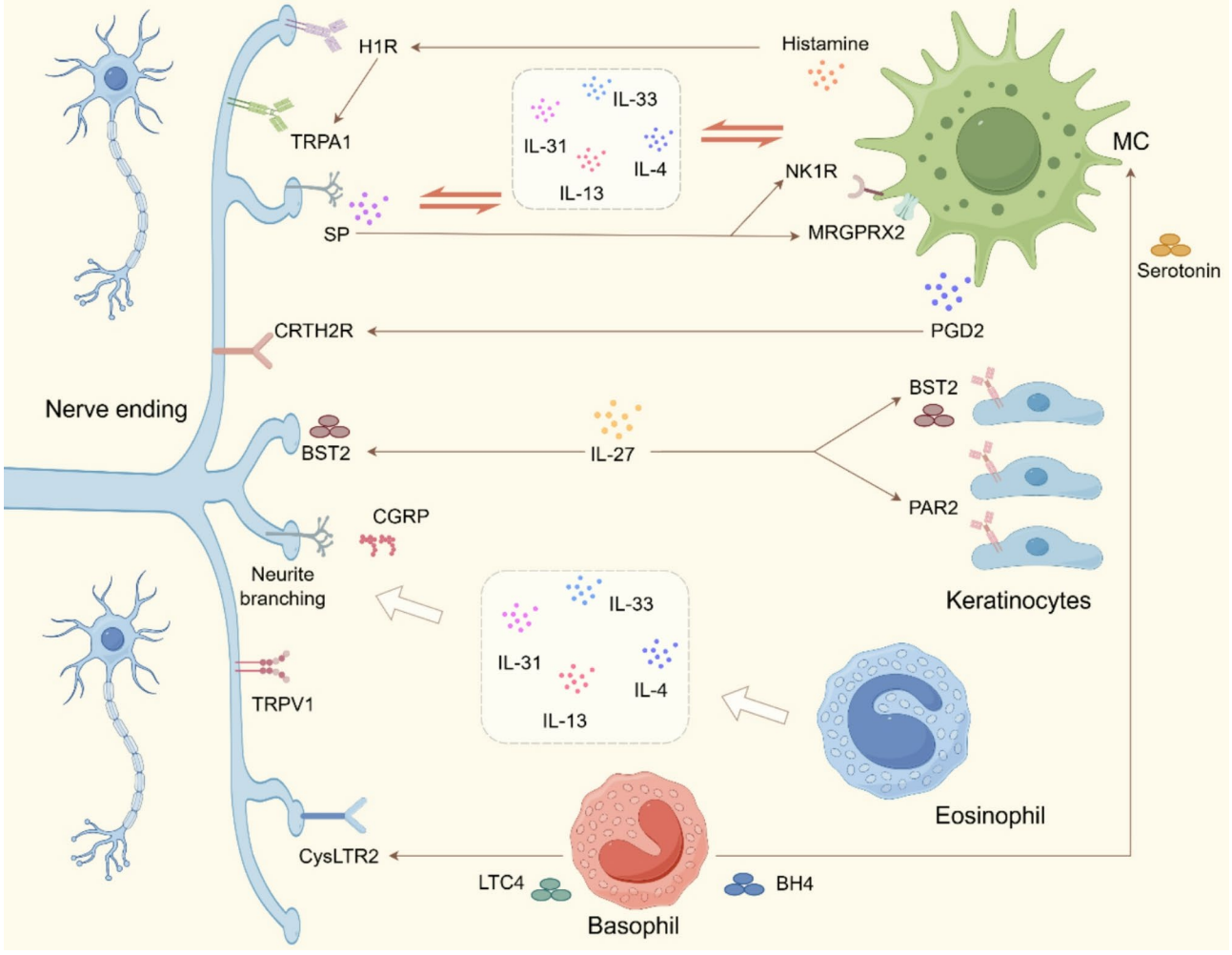


**Fig. 4** Bidirectional Interaction Between Sensory Neurons and Immune Cells in CU. The figure was created using Figdraw (ID: SYAPT61556). Sensory neurons interact bidirectionally with immune cells, releasing neuropeptides and activating receptors such as TRPV1 and TRPA1, thereby enhancing neurogenic inflammation and itch responses

**Table 3** Neuroimmuity-related animal models of CU

| Animals | Type | Drugs | Methods | Manifestations | References |
|---|---|---|---|---|---|
| Balb/c mice | CU | SP | Mice were sensitized on days 14 and 21 with subcutaneous injections of 0.5 mL SP (30 μg/mL) in saline at multiple sites. | Skin wheals, itching and scratching of mouse skin | [113] |
| Balb/c mice | CU | SP | Mice in the model group were sensitized by subcutaneous injection of 0.5 mL SP (30 μg/mL) on Days 0, 7, 14, and 21. On the 25th day, 0.2 mL SP (30 μg/mL) was injected into the tail vein of the mice. | Paw swelling | [114] |
| Male C57BL/6 mice | CSU | Ovalbumin combined with SP | OVA (20 μg/ml) was injected into the left paw. after anesthesia, the mice were injected with 5 μl SP (30 μ g/ml) for 15 min directly into the left paw. | Paw swelling | [66] |

responses [66]. These highlight the interaction between SP and MCs, but its effects on eosinophils, basophils, and mesenchymal cells in animal models need further study. These SP-related neuroimmune CU models are listed in Table 3.

## Psychological factors related to CU

Mind-body influences are bidirectional [115]. CU patients frequently experience elevated levels of psychological disorders [116–118]. The repeated attacks of skin diseases also bring huge pressure to patients, leading to more depression, impatience, tension, and anxiety. Numerous mediators enhance sensory innervation, stimulate the production of additional pruritogenic agents,

sustain neurogenic inflammation, and reduce the threshold for itch perception [119]. However, the application of relevant animal models has not been reported.

#### Current states of psychological factors linked to CU

Psychological factors are internal mental processes affecting emotions, thoughts, and behaviors, including stress and emotional responses. While stress causes CIndU, CSU is also associated with psychiatric comorbidities [120]. Psychological and emotional stress may also precede the onset of CSU [121]. Nearly 16% of CU patients suffered from mental disorders [122]. They exhibit significantly poorer mental and physical health, with increased depression, anxiety, and sleep issues [123, 124]. Patients with CU, especially CSU, have a higher prevalence of psychiatric disorders and medication use, with increased risk and severity of depression and anxiety correlating with the severity of urticaria [117, 125–127]. CSU is more strongly associated with anxiety in individuals aged 18–29 and those with high socioeconomic status, while the link between CSU and depression is strongest in the 50–69 age group and among those with low socioeconomic status [128]. The urticaria control test moderately negatively correlates with quality-of-life scores, the Patient Health Questionnaire-9, and the Beirut Distress Scale-22. Patients with the lowest scores experience the greatest impact on quality of life and depression [129]. Therefore, psychological support and patient education are as important as traditional medication in controlling disease activity and prolonging remission [130].

#### Current state of psychological factors in CU models

There are no widely reported CU models that specifically incorporate psychological stress. Instead, existing studies primarily focus on psychological stress models in general. The Chronic Mild Stress model subjects animals to mild stressors, mimicking human chronic stress, and is useful for examining behavioral and neurochemical changes. It reveals stress-induced dysfunctions similar to those in humans, such as altered reward processing and stress hormone regulation [131]. However, translating these findings to humans is limited, as the models often use simplified stimuli. In humans, psychological issues like anxiety, depression, and stress in CU are tied to cognitive and emotional aspects such as self-esteem, peer interactions, and emotional regulation, which are hard to replicate in animal models.

Some stress-related skin disease models may offer valuable insights for developing stress-related CU models. Chronic allergic contact dermatitis was induced through repeated sensitizing agent applications and social isolation to simulate the interaction between psychological stress and skin inflammation [132]. Repeated immobilization stress and social isolation stress have been used in atopic dermatitis research to explore the link between stress and its development [133, 134].

### Interaction between immune, neurological, and psychological factors

During embryonic development, both the skin and the nervous system originate from the ectoderm, underscoring their interconnected roles in responding to environmental stimuli. The interaction between the nervous and immune systems is implicated in dermatological conditions, particularly CU, where neural factors are increasingly associated with depression, anxiety, and pruritus. These are shown in Fig. 5.

#### Neural mechanisms of depression, anxiety, and itch in CU

In CU, the prefrontal cortex, cerebellum, and thalamus are implicated in depression and anxiety. The intensity of serotonin transporter protein expression in CSU patients was not significantly associated with the severity of depression, but was significantly associated with the severity of anxiety [135]. The dorsolateral prefrontal cortex is crucial for emotional regulation and cognitive control, while the cerebellum and thalamus, beyond motor functions, influence emotional processing and mood disorders in CSU [136–139].

Research on the neural mechanisms of depression, anxiety, and itching in CU is still limited. CU is also a pruritic skin disease, and other pruritic mechanisms may provide valuable insights for exploring the neural mechanisms underlying depression, anxiety, and itching in CU. Itch signals move from the PBN to the thalamus and somatosensory cortex, mapping the location of itch and linking it to emotional and reward systems [140]. Neurons expressing CGRP in the lateral external subdivision of the PBN are activated by various threat stimuli and transmit this information to the laterocapsular subdivision of the central amygdala (CeA), modulating affective itch and scratching behavior [141]. Chronic itch and addiction share neural circuits, with both activating the dopamine system in brain reward and motivation pathways, such as the ventral tegmental area (VTA) and nucleus accumbents (NAc), making scratching behavior similar to addictive behavior and forming a hard-to-control vicious cycle [142]. Brain structures related to emotion, such as the limbic system and periaqueductal gray, which modulate itch through descending facilitation, are crucial in stress-induced itch [143]. Activation of the amygdala and hippocampus often occurs concurrently in itch studies, suggesting the role of past itch experiences in itch-related anxiety [144].

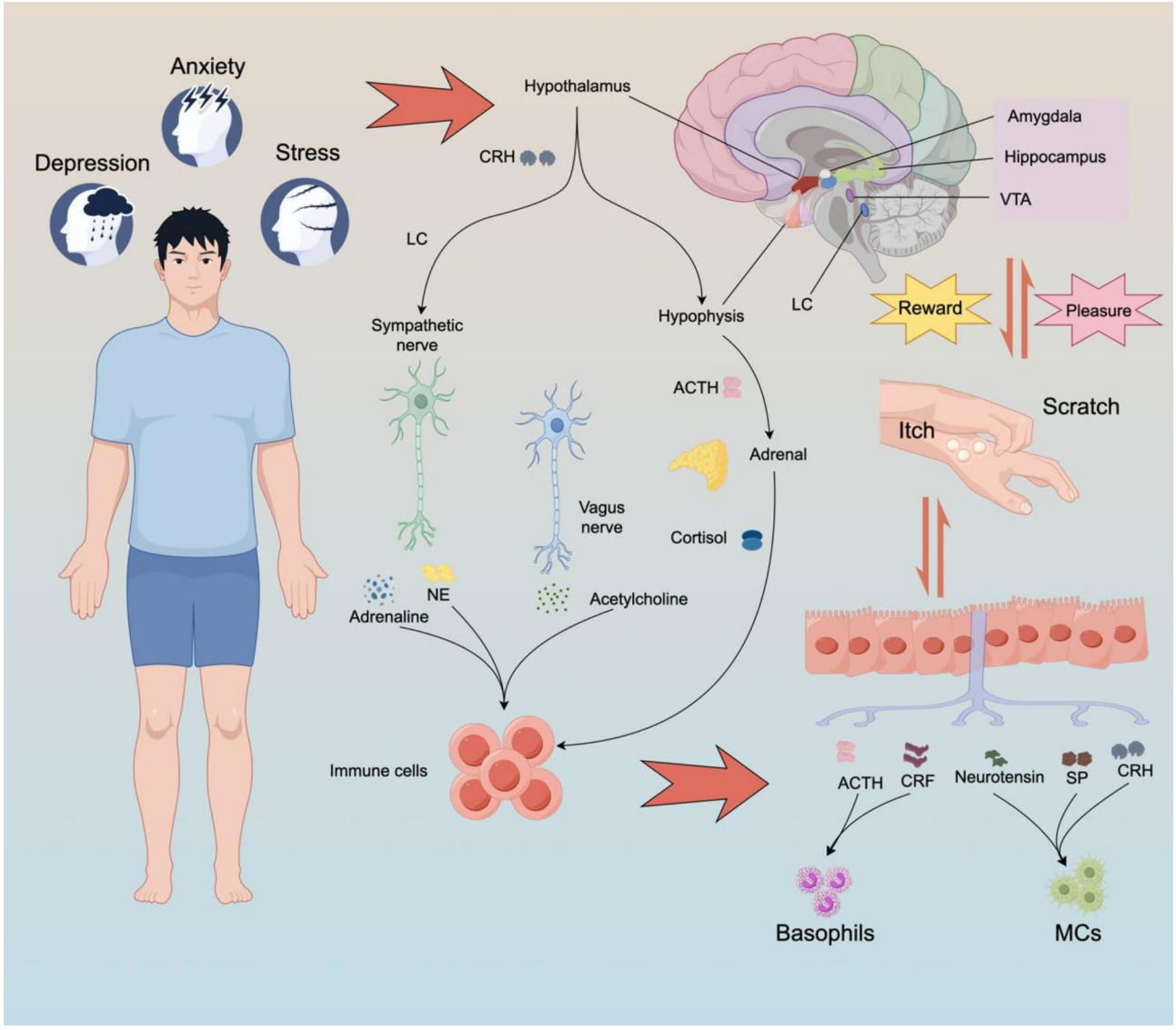


**Fig. 5** Emotional abnormalities interact with skin itching. The figure was created using Figdraw (ID: RSSTAad4de). Anxiety, depression, and stress are correlated with the development of CU. They overstimulate the HPA axis and the brainstem LC-NE/ SNS-SAM systems, resulting in the release of CRH, ACTH, cortisol, LC, adrenaline, NE, acetylcholine, and other substances. These secretions activate immune cells to produce cytokines, which can trigger itching. Moreover, the act of scratching elicits pleasure that is stored in memory by various regions of the brain, including the hippocampus, VTA, and amygdala, ultimately impacting behavior by reinforcing the habit of scratching

### Psychosomatic factors affect immune cells through the nervous system

Under stress, various central nervous system loci exhibit plasticity and undergo remodeling, mediated by increased glutamatergic and noradrenergic activity, cytokines, and glucocorticoids, regulated by the HPA axis and the brainstem LC-norepinephrine (NE)/ssympathetic nervous/sympatho-adrenomedullary systems (SNS-SAM) systems [145]. Interleukin-6 (IL-6), interleukin-1 (IL-1) and interferon-γ are activated, and corticosteroid-releasing hormone (CRH)-proopiomelanocortin-adrenocorticotropic hormone (ACTH)-corticosteroid axis is excited [146]. Furthermore, chronic stress appears to increase nerve fiber density in the dermis, MCs, NGF, and CGRP [147]. This interaction exacerbates symptoms and promoting the persistence of CU [148].

#### *HPA axis and hormonal regulation in stress and inflammation*

The hypothalamus releases CRH, stimulating the anterior pituitary to secrete ACTH. Then the adrenal glands are prompted to produce cortisol, a primary stress hormone. While cortisol regulates the immune system and has anti-inflammatory effects under normal conditions, the body may develop a tolerance to high cortisol levels, leading to an overactivation of the immune system and

increased inflammatory responses [149–151]. Both anxiety and depressive disorders influence cortisol responses to stress [152]. Inhibiting cellular retinoic acid-binding protein 1 within the hypothalamus and pituitary glands attenuates acute stress-induced anxiety-like behaviors and markedly decreases corticosterone concentrations [153]. Adrenaline and NE are released from the adrenal medulla, causing characteristic vasoconstriction and MC degranulation [154]. Stress-induced MC degranulation depends on CRH but may also involve the role of SP and neurotensin [155]. CRH also causes blood vessel dilation in human skin through an MC-dependent pathway [156]. Moreover, both corticotropin-releasing factor (CRF) and ACTH have been confirmed to activate basophils [157]. In addition, anxious depression was associated with a decreased basophil subfraction [158].

#### *Autonomic nervous system in emotion regulation, immune response, and CU*

The activity of the ANS is fundamental in the regulation of emotion and motivated behavior [159]. The potential facilitative role of the SNS is promoting hostile reactivity and emotion-driven impulsivity in individuals with higher levels of neuroticism [160]. Immune function may be impacted in various conditions marked by heightened sympathetic activity, with these changes potentially linked to dysregulation of CRH in the brain [161]. Additionally, autonomic nerves release neuromediators such as adrenaline and norepinephrine that communicate with both innate and adaptive immune cells, activating specific receptors on numerous target cells in the skin [162, 163]. In CU, activating the SNS stimulates immune cells, especially MCs, releasing inflammatory mediators [164, 165]. The parasympathetic nervous system, particularly through the vagus nerve, influences immune responses by releasing neurotransmitters like acetylcholine. Cholinergic urticaria is a common type of CIndU that presents with pruritic wheals and angioedema triggered by perspiration. The diminished expression of acetylcholine receptor M3 and acetylcholinesterase in individuals with impaired sweating may be either the etiology or a resultant factor of cholinergic urticaria [166].

In addition, the dysregulation of the stress axis in the presence of heightened sympathetic tone and diminished parasympathetic activity, may exacerbate inflammation through direct impacts on brain regions essential for fear and anxiety regulation [167]. Anxiety and depression also cause dysfunction of the blood-brain barrier, which is maked by increased permeability related to inflammation [168].

### Neuro-cutaneous interactions of embryonic origins and implications for skin disease modeling

The embryonic origins of the skin and nervous system are intricately linked, tracing back to the early stages of embryonic development. Both the skin and the nervous system originate from the ectoderm, the outermost of the three primary germ layers formed during early embryogenesis [169]. This common origin underlies their integrated roles in sensing and responding to environmental stimuli. The intrinsic transcription factors, such as Neurogenin 1 and Runx1, and extrinsic neurotrophic factors including NGF and glial cell derived neurotrophic factor, work together to drive the differentiation of pain and itch receptors from common embryonic precursor cells into distinct functional subtypes [170]. The immune system, while primarily arising from the mesoderm, interacts extensively with both the skin and nervous system to modulate responses to injury, infection, and inflammation [171]. Sensory neurons can activate reflex arcs to induce anticipatory immune responses in adjacent tissues, priming them to better defend against potential infections [172]. As these balances are disrupted, the likelihood of itching, edema, and hives increases.

By utilizing advanced 3D imaging techniques, an unprecedented and detailed cellular map of early human development is provided [173]. Integrating components of the neuro-immune-cutaneous system into the design of human skin equivalents allows for more accurate modeling of physiological skin responses, particularly in the study of skin diseases involving neuro-immune interactions [174]. The development of tissue-engineered innervated skin models offers a more precise and physiologically relevant platform for studying neuro-cutaneous disorders, improving drug screening, disease mechanism understanding, and the creation of therapeutic interventions [175].

## Discussion and future directions

### Limitations of current research and the need for enhanced translational models in CU

In human CU, MCs and basophils are crucial in releasing histamines and other pro-inflammatory mediators, contributing to the characteristic symptoms of wheals, angioedema, and pruritus. However, the immune responses observed in animal models, particularly murine systems, diverge significantly from those in humans. The distribution and density of MCs differ between human and murine skin, resulting in different activation thresholds and responses to stimuli like IgE cross-linking.

Anxiety, depression, and stress are common in human CU, worsening the condition and making it chronic by causing neuroimmune dysregulation that leads to persistent itching and inflammation. Although stress can be simulated in animal models, they fail to capture the

complex interplay between psychological stress and immune function seen in humans. Stress-induced activation of the HPA axis and ANS has downstream effects on immune cells, particularly MCs and basophils. This neuroimmune connection is difficult to model in animals, where the emotional and cognitive components of stress differ significantly from humans. Thus, future models should employ human-derived tissues, advanced in vitro systems like organoids, or humanized animal models to replicate human immune responses in CU.

### Diagnosis and treatment strategy of CU under the guidance of mind-body model

During the diagnostic process of CU, a comprehensive assessment incorporating neurological, immunological, and psychological biomarkers is essential. Psychological status and stress levels can be evaluated using tools such as the Symptom Checklist-90 and the Perceived Social Support Scale. For patients with high stress or psychological issues, consider using detailed assessments like the Eysenck Personality Questionnaire, the Chronic Urticaria Quality of Life Questionnaire, and stress-specific questionnaires. This comprehensive approach improves diagnostic accuracy and aids in personalized treatment.

Current treatments for CU, such as antihistamines, omalizumab, and cyclosporine, show variable efficacy under psychological stress. Therefore, integrating psychological and physical treatments, such as cognitive-behavioral therapy, relaxation training, and stress management, could be more effective. In addition, considering individual differences in psychological stress responses, treatment should emphasize personalized approaches. Combining different therapeutic agents based on the patient's specific disease characteristics and comorbidities is emerging as a strategy to improve treatment outcomes and address the complex nature of CU [176].

Complementary and alternative therapies may also be an effective means of alleviating CU symptoms and regulating negative emotions. The patients went through psychological counseling, improving these disorders [177]. Acupuncture is an external therapy in traditional Chinese medicine. Randomized clinical trials has shown that it can produce a greater improvement in the Weekly Urticaria Activity Score, and regulate humoral immunity markers and serum total IgE levels [178, 179]. Its antidepressant-like effects appear to be involved in the inhibition of NLRP3 inflammasome activation and apoptosis in the prefrontal cortex [180]. Moreover, it can partly suppress the neuroinflammation induced by the Toll-like receptor 4 signaling pathway [181]. The combination of acupuncture, pricking, and cupping therapy has shown great efficacy in treating CSU by reducing symptoms and negative emotions, enhancing quality of life and sleep, and balancing Th1/Th2 cytokines [182].

## Conclusion

CU is a multifactorial condition involving complex neuroimmune and psychological interactions. Current treatments, while effective for some, often fail to address the full spectrum of contributing factors, particularly psychological comorbidities like anxiety and stress, which exacerbate CU symptoms. The limitations of existing animal models, which cannot fully replicate human immune and neuropsychological responses, hinder the development of more targeted therapies. Future research should focus on creating advanced models that integrate neuroimmune mechanisms and psychological factors, while incorporating complementary therapies such as acupuncture to provide more holistic and effective treatment strategies.

#### Abbreviations

| | |
|---|---|
| CU | Chronic urticaria |
| IgE | Immunoglobulin E |
| MCs | Mast cells |
| HPA | Hypothalamic-pituitary-adrenal |
| ANS | Autonomic nervous system |
| CIndU | Chronic inducible urticaria |
| CSU | Chronic spontaneous urticaria |
| FcεRI | High-affinity IgE receptor |
| MRGPRX2 | MAS-related G protein-coupled receptor X2 |
| TF | Tissue factor |
| C5a | Complement 5a |
| C5aR | C5a receptor |
| KIT | Stem-cell factor receptor |
| PAR1 | Protease-activated receptor 1 |
| PAR2 | Protease-activated receptor 2 |
| PI3K | Phosphoinositide 3-kinase |
| Akt | Protein kinase B |
| NF-κB | Nuclear factor kappa-B |
| IL-4 | Interleukin-4 |
| IL-13 | Interleukin-13 |
| IL-31 | Interleukin-31 |
| SP | Substance P |
| IL-3 | Interleukin-3 |
| PGE | Prostaglandin E |
| EPO | Eosinophil peroxidase |
| ECP | Eosinophil cationic protein |
| TNF-α | Tumor necrosis factor-α |
| CGRP | Calcitonin gene-related peptide |
| IgG | Immunoglobulin G |
| VEGF | Vascular endothelial growth factor |
| BCR | B-cell receptor |
| IL-17 | Interleukin-17 |
| IL-21 | Interleukin-21 |
| Treg | Regulatory T |
| TGF-β1 | Transforming growth factor-β1 |
| IL-35 | Interleukin-35 |
| BR1 | Bradykinin receptor 1 |
| BTK | Bruton tyrosine kinase |
| OVA | Ovalbumin |
| TMA | Trimellitic anhydride |
| JAK | Janus kinase |
| STAT | Signal transducer and activator of transcription |
| CAU | Chronic autoimmune urticaria |
| IL-9 | Interleukin-9 |
| IL-10 | Interleukin-10 |
| DNP | 2,4-Dinitrophenol |

| | |
|---|---|
| DNFB | 2,4-dinitrofluorobenzene |
| IL-33 | Interleukin-33 |
| SNARE | Soluble N-ethylmaleimide-sensitive factor attachment protein receptor |
| mGluR5 | Metabotropic glutamate receptor 5 |
| MrgprA3 | Mas-related G protein-coupled receptor A3 |
| GRP | Gastrin-releasing peptide |
| GRPR | Gastrin-releasing peptide receptor |
| GABA | Gamma-aminobutyric acid |
| RVM | Rostral ventromedial medulla |
| IL-1β | Interleukin-1β |
| NLRP3 | NOD-like receptor thermal protein domain associated protein 3 |
| IL-1R1 | Type 1 IL-1 receptor |
| PAG | Periaqueductal gray |
| CB1 | Cannabinoid receptor type 1 |
| 5-HT | 5-hydroxytryptamine |
| LC | Locus coeruleus |
| NAergic | Noradrenergic |
| α1AAR | α1A-adrenergic receptors |
| Ucn3 | Urocortin 3 |
| LTMRs | Low-threshold mechanoreceptors |
| NPY | neuropeptide Y |
| NPY1R | Neuropeptide Y1 receptor |
| PBN | Parabrachial nucleus |
| Calcrl | Calcitonin receptor like receptor |
| FoxP2 | Forkhead box protein P2 |
| TRPV1 | Transient receptor potential vanilloid 1 |
| TRPA1 | Transient receptor potential ankyrin 1 |
| PGD2 | Prostaglandin D2 |
| H1R | H1 receptor |
| CRTH2R | Chemoattractant receptor-homologous molecule expressed on Th2 cells receptor |
| NK1R | Neurokinin-1 receptor |
| IL-27 | Interleukin-27 |
| BST2 | Bone marrow stromal antigen 2 |
| NGF | Nerve growth factor |
| LTC4 | Leukotriene C4 |
| CysLTR2 | Cysteinyl leukotriene receptor 2 |
| BH4 | Tetrahydrobiopterin |
| NGF | Nerve growth factor |
| CeA | Central amygdala |
| VTA | Ventral tegmental area |
| NAc | Nucleus accumbens |
| NE | Norepinephrine |
| SNS-SAM | sympathetic nervous/sympatho-adrenomedullary systems |
| IL-6 | Interleukin-6 |
| IL-1 | Interleukin-1 |
| CRH | Corticosteroid-releasing hormone |
| ACTH | Adrenocorticotropic hormone |
| CRF | Corticotropin-releasing factor |

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Shurui Yang and Li Chen made equal contributions and are listed as co-first authors. Shurui Yang and Li Chen: conceptualization. Haiming Zhang, Yanjuan Song, Wenyan Wang, Zhengbo Hu, Siyu Wang, Liuyang Huang, Yayuan Wang and Song Wu: literature search. Shurui Yang, Li Chen, Haiming Zhang, Yanjuan Song, Wenyan Wang, Zhengbo Hu, Siyu Wang, Liuyang Huang, Yayuan Wang and Song Wu: writing—original draft. Rui Chen and Fengxia Liang: writing—review and editing.

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**Data availability**
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## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
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**Competing interests**
The authors declare no competing interests.

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