



# Psychological Stress and Urticaria: Pathophysiologic and Therapeutic Updates

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## Abstract

**Purpose of review** The goal of this review is to examine the relationship between psychological stress and chronic urticaria (CU), focusing on the underlying mechanisms and potential therapeutic interventions. The paper seeks to answer how stress exacerbates CU and the neuro-immunological pathways involved, providing insight into improving therapeutic strategies by considering the psychological dimensions of the disease.

**Recent findings** Recent studies highlight the significant role of stress in aggravating CU through the dysregulation of the hypothalamic-pituitary-adrenal axis and neurogenic inflammation. Increased levels of neuropeptides like substance P and calcitonin gene-related peptide, as well as upregulated expression of the MRGPRX2 receptor, are implicated in the neuro-immune interactions that worsen CU symptoms. Additionally, psychological distress has been linked to poorer disease outcomes, with stress management strategies and psychopharmacological interventions showing promise in reducing disease severity.

**Summary** This review concludes that stress significantly contributes to the exacerbation of CU through neuro-immune pathways, suggesting the need for holistic treatment approaches. Addressing both the physical and psychological aspects of CU may improve disease management and patient outcomes. Future research should focus on further elucidating the connection between stress and CU and developing targeted therapies that integrate stress reduction techniques into standard care.

**Keywords** Chronic urticaria · Psychological stress · Neuroimmunology · Mental health · Neurotransmitters · Quality of life

## Abbreviation

CGRP Calcitonin Gene-Related Peptide  
CU Chronic urticaria  
CSU Chronic spontaneous urticaria

CIndU Chronic inducible urticaria  
HC Healthy controls  
HPA Hypothalamic-pituitary-adrenal  
MRGPRX2 Mas-related G protein-coupled receptor X2

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SP	Substance P
SAM	Sympathetic-adreno-medullar
MC	Mast cells
VIP	Vasoactive Intestinal Peptide
TRPV1	Transient Receptor Potential Vanilloid 1
5-HT	5-hydroxytryptamine

## Introduction

Chronic urticaria (CU) is a persistent skin condition marked by recurrent itchy hives and angioedema lasting for more than six weeks. It can be classified into two subtypes: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) [1]. CU significantly impacts the quality of life (QoL) and healthcare systems [2]. It affects work and school performance and disrupts sleep quality. The disease imposes a significant burden on both patients and society. The burden stems from various factors, including medication costs, outpatient visits, emergency room treatments, hospitalizations, laboratory tests, and lost productivity, resulting in an economic strain. Furthermore, CU is associated with emotional distress, including anxiety, depression, and stress, which are thought to contribute to the persistence of the condition [3].

Mast cells (MCs) play an important role in the immune response by detecting external stimuli such as pathogens and toxins with the subsequent release of mediators that cause sensory nerve activation, vasodilation, extravasation, and the recruitment of circulating inflammatory cells including eosinophils and basophils [4, 5]. These cellular events lead to the formation of wheals and angioedema; however the most important question is how MCs are activated. Currently, the main mechanism responsible for the activation of MCs in CSU is thought to be the autoimmune mechanism [6, 7]. When IgE antibodies target autoantigens (autoallergens), this is defined as type I autoimmune (autoallergic) CSU (aaCSU) [8]. Conversely, in type IIb autoimmune CSU, patients have MCs-activating IgG autoantibodies directed against IgE or its receptor FcεRI [9]. However, 16% of CU patients don't have any of these autoantibodies [7].

There are many reports on the involvement of IgE-independent reactions, mainly to food additives and drugs [10] in CSU. However, it is not well understood yet if they act via the Mas-related G protein-coupled receptor X2 (MRG-PRX2). This receptor is highly expressed in human skin and has attracted much interest recently. It can be activated by many different ligands including neuropeptides released from sensory neurons such as cortistatin (CST) and substance P (SP) and mediators released from eosinophils which altogether contribute to the pathogenesis of CSU [4, 11]. Additionally, activated skin sensory nerves and infiltrating cells play an important role in the inflammatory response

initiated by the degranulation of skin MCs [3]. While autoimmunity being the major mechanism, factors such as foods, infection, pseudo allergies, vaccination [12–14], medications, and stress [9] are the modulating factors that exacerbate urticaria [15, 16]. Additionally, there is a wide range of comorbidities associated with CU being the most common: psychiatric, atopic and autoimmune diseases [17–20]. A recent meta-analysis found that almost one out of three CU patients have at least one underlying psychiatric disorder, sleep–wake disorders, followed by anxiety and mood disorders, including depression are frequently identified (pooled prevalence 36.7%, 30.6% and 29.4% respectively) [21]. Moreover, mental health was negatively correlated with quality of life and more severe disease, suggesting a potential bidirectional relationship between CU and psychiatric conditions [22–24]. A recent study revealed that stress was associated with an increase in chronic urticaria quality of life scores, additionally can affect exacerbation of urticaria wheals and itch intensity [23].

However, the underlying mechanism of stress and its association with urticaria remains to be identified. Currently, we are aware that “brain-skin connection” may contribute to stress causing aggravation of urticaria [25], and chronic stress induce alteration of the hypothalamic–pituitary–adrenal (HPA) axis function and the sympathetic nervous system [26] and lead to changes in the functioning of the immune cells.

The main goal of this paper is to offer a comprehensive overview of the occurrence and mechanisms of physiological stress in CU, aiming to enhance our understanding of its effects on patients. Additionally, it seeks to identify gaps in current research to pave the way for improved patient outcomes through targeted therapies and a holistic approach that includes addressing patients' psychological well-being.

## Stress and immunity: general background

The term “stress” encompasses situations where the demands of the environment exceed an individual's perceived ability to manage them both psychologically and physiologically [27]. Any physical or psychological stimuli which are called as stressors that disrupt homeostasis results in stress response [28], and many different spectrums of dermatologic conditions can be exacerbated by these stimuli [29, 30]. The brain is a stress receiver and initiator of stress responses. The brain initiates stress response and then transmits information to the periphery through various mediators [26]. The physiology of stress response in humans basically has 2 main components; a rapid and short-term response mediated by the sympathetic-adreno-medullar (SAM) axis, and a slow and short-/long-term response mediated by the HPA axis. The cognitive, emotional, and biological reactions triggered by stressful events are known as stress responses [31].

## Acute stress response

Upon facing an acutely stressful situation, SAM is activated which leads to secretion of catecholamines from central nervous system and adrenal glands [32]. Activation of  $\alpha$ - and  $\beta$ -adrenergic receptors leads to vasoconstriction, increased blood pressure, tachycardia and elevated blood glucose levels to produce “fight or flight” response [28].

Several studies showed that acute stress could affect immune system through increased secretion of IL-6, TNF- $\alpha$ , and IL-1 $\beta$  [33]. It was also shown that short-term stress response orchestrates the movement of immune cells and redistributes all major leukocytes among different body compartments, in animal models [34]. Poller et al. showed that acute stress response mobilizes neutrophils out of the bone marrow, and temporarily diverts lymphocytes and monocytes from peripheral organs to bone marrow [35]. Acute stress causes rapid mobilization of neutrophils through skeletal-muscle-derived neutrophil-attracting chemokines (CXCL1). Stress-induced bone-marrow homing of lymphocytes and monocytes is CXCR4 dependent, which is a bone marrow retention and homing factor and regulated by glucocorticoids [36].

## Chronic stress response and the psycho-neuro-endocrine-immunology axis

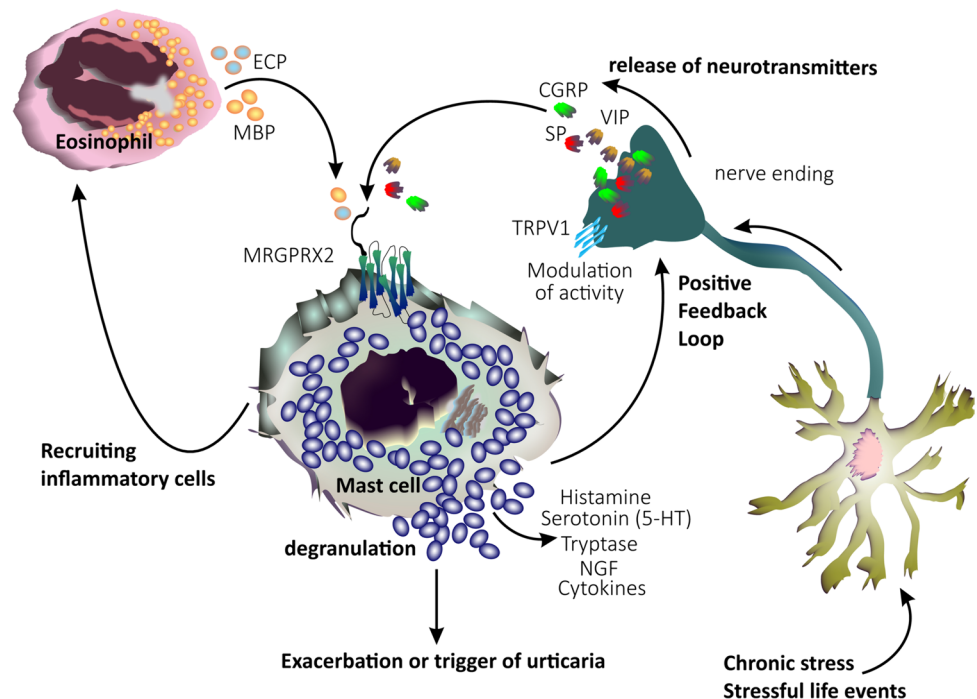
Longstanding exposure to stressors causes chronic stress response which can lead to cumulative physiological and psychological effects. Prolonged stress can cause significant

alterations in both innate and adaptive immune responses, mostly through the action of neuroendocrine mediators from the SAM and HPA axes [37]. Stress results in a corticotrophin-releasing hormone (CRH) release from the hypothalamus. CRH activates adrenocorticotropin (ACTH) secretion from the anterior pituitary gland, which in turn stimulates adrenal cortex to produce and release corticosteroids. As a feedback response, increased cortisol levels in blood stream leads to the inhibition of CRH and ACTH secretion [36]. In stressful situations, cortisol is secreted as the body's defense response. Cortisol protects the body from an excessive immune response [38]. Cortisol and catecholamines modify the balance between Th1 and Th2 responses [39–41]. Chronic stress increases Th2 responses and reduces NK-cell activity [42]. It should also be noted that chronic stress results in the dysregulation of the HPA axis, namely HPA axis fatigue and in the end lead to hypocortisolism and sustained sympathetic nervous system hyperactivity.

## Mast cells and their role in neurogenic inflammation

Psychological stress can trigger the release of neuropeptides like substance P, which can activate mast cells through neuroendocrine pathways, linking stress to neurogenic inflammation [26]. Neurogenic inflammation in skin involves a bidirectional communication between MCs and sensory nerves [43]. The anatomical distribution of MCs and their abundance close to nerve endings, blood vessels, and lymphatic vessels, allow them to respond quickly to environmental changes and play a key role in inflammation [44, 45].

**Fig. 1** Chronic stress and stressful life events stimulate neurons which induce the release of neurotransmitters like SP, VIP, and CGRP from neuron endings. The released transmitters can directly activate and degranulate MCs due to close proximity to (dermal) MCs. Released histamine, serotonin, tryptase, NGF, and cytokines stimulate neurons and induce the release of more transmitters, and complete a positive loop of activation between MCs and neurons. The released mediators also promote the recruitment of inflammatory cells like neutrophils and eosinophils to the site. The latter release ECP and MBP which like transmitters activate MCs through acting on MRGPRX2. MC-release mediators trigger urticaria or worsen the condition.



The proximity of MCs and neurons in the skin enables them to have bidirectional interactions both in physiological and pathological conditions [46, 47].

In urticaria, as mentioned earlier, MCs become activated via autoantibodies in autoallergic or autoimmune mechanisms and release proinflammatory mediators. Activation of MCs and consequently their degranulation is closely linked not only to vasoactive and proinflammatory effects but additionally to sensory nerve stimulation [48].

In this regard, histamine, tryptase, Serotonin (5-hydroxytryptamine or 5-HT), TNF, and nerve growth factor (NGF) released from MCs stimulate neurons. Mast cell mediators can sensitize nociceptors by interacting with specific receptors (e.g., H1R) and modulating the activity of ion channels like TRPV1 [43, 49, 50] and induce their release of neuropeptides like Substance P (SP), and Vasoactive Intestinal Peptide (VIP) which are also capable of activating MCs [51]. The activation of mast cells by neurons and subsequent activation of neurons by mast cell mediators creates a positive feedback loop, amplifying and sustaining the neurogenic inflammatory response. SP once released from neurons degranulates MCs and induces the release of histamine which in turn acts through its receptors on sensory nerve endings and evokes the production of neurotransmitters which worsen the condition [52] (Fig. 1). Moreover, SP-induced vascular endothelial growth factor (VEGF) release from MCs, contributes to endothelial cell proliferation and vascularization which, consequently, promotes inflammation [52, 53]. The effectiveness of these neuropeptides makes them possible to be used as MC activators for in vitro studies of MC degranulation [54].

One key receptor in charge of MC responsiveness to neuropeptides is Mas-related G-protein coupled receptor member X2 (MRGPRX2) which is highly expressed on human skin MCs [55].

In addition to the direct interaction of MCs and neurons in neuroinflammation, MCs may use other mechanisms to aggravate the condition. MC-released mediators play a role in the chemoattraction of inflammatory cells (eosinophils, neutrophils, monocytes, and macrophages) [56]. Of these cells, eosinophils are recruited by IL-5, and histamine (through H4R) [4, 57]. Accumulation of eosinophils in inflammatory sites is accompanied by their degranulation and release of active components that have immunological biofunction on other cells including MCs. Interestingly, MRGPRX2 may be activated by several eosinophil-released mediators mainly Major Basic Protein (MBP) and eosinophil cationic protein (ECP) [58].

From a clinical point of view, the levels of these neuropeptides increase and MRGPRX2 expression is upregulated in the skin of patients with CSU, AD, rosacea, psoriasis, and chronic pruritus highlighting their contribution to amplifying neuroinflammation [52, 59–61] and may act as future targets for treatment.

## Stress and chronic urticaria

The skin is both an immediate stress perceiver and a target of stress responses. Stressors typically occur over the following timescales: acute stressors, chronic stressors, life events and daily events/hassles [31]. Studies have demonstrated that both chronic stressors and significant life events contribute to the development of CU, whereas the impact of acute stressors and daily hassles have not been extensively researched. However, Engel-Yeger et al. [62] found that patients with CSU have a heightened acute stress response evidenced by stronger electromyography responses and more frequent eye blinks to auditory startles compared to healthy controls. They also had faster and prolonged electrodermal activity (EDA) responses, indicating a heightened reactivity of the sympathetic nervous system. Increased skin blood flow during stress exposure, suggested a less efficient adaptation to stress.

Reflecting the impact of chronic stress and HPA axis activation on the pathophysiology of CU, Varghese et al. [63] demonstrated a significant reduction in basal cortisol levels in CU patients, which was more pronounced with increasing disease severity and in cases of autoimmune urticaria. Hypocortisolism was significantly associated with higher levels of hs-CRP, IL-18, PSLE, and DHUS-R scores, as well as with the duration and severity of urticaria symptoms. The findings suggest a significant role of chronic stress in the pathogenesis of CU, contributing to a vicious cycle of inflammation and hypocortisolism. Likewise, increased psychological distress and poor quality of sleep and life may, in turn, affect the functioning of the HPA axis resulting in cardiac dysautonomia and its associated morbidities [11, 12].

Other studies focused on the effect of urticaria severity on patient stress levels have found a positive correlation, indicating that increased severity of chronic urticaria is associated with heightened stress and distress among patients, through persistent physical symptoms, disturbed sleep, emotional and psychological burdens, impaired quality of life, and economic impacts (Table 1). A possible explanation for this is that stress can trigger the release of neuropeptides such as SP and CGRP, which subsequently activate mast cells and amplify inflammatory responses [63–66].

A stressful life event is defined as an unwanted, unpredictable occurrence that can involve an individual's finances, work, social relationships, health, and housing. Such events can negatively impact an individual's physical and psychological well-being [81].

In a web-based survey of 114 Canadian allergists and immunologists, 58.4% believed that life events contribute to the pathogenesis of chronic urticaria (CU) [82]. Multiple studies support this link, showing higher rates of stressful events preceding disease onset in CU patients compared to controls (Table 1). For instance, 90% of CU patients reported

**Table 1** Studies describing the link between stress and urticaria

Manuscript	Methodology and scales/questionnaires/biomarkers used	Key takeaways
<p>Studies suggesting stress or previous psychological trauma as predisposing factors in the development of CU</p> <p>Yang et al. (2005, China) [67]</p>	<p>75 CSU/133 controls</p> <p>Major Life Events Survey</p> <p>Somatic Symptoms Checklist</p> <p>Insomnia Scale</p> <p>Irregularity Index of Daily Life</p> <p>Ego-function Index, Family Support Index, and Psychosomatic Symptoms Inventory</p> <p>Ways of Coping Checklists</p>	<p>In the six months preceding disease onset, patients with CIU experienced significantly more life events, higher subjective impact from these events, more somatic symptoms, severe insomnia, less family support, and more negative coping tendencies compared to controls</p> <p>Good ego-function, effective coping strategies, and strong family support were associated with a decreased frequency of urticaria</p> <p>Insomnia might be the most critical psychosomatic symptom predisposing individuals to CIU</p> <p>Stress is a significant risk factor for the development of chronic idiopathic urticaria. Positive coping strategies and strong family support appear to mitigate this risk</p>
<p>Elçin et al. (2024, Turkey) [68]</p>	<p>42 CSU / 42 controls</p> <p>Life Events Checklist for DSM-5 (LEC-5)</p> <p>Depression Anxiety Stress Scale-42 (DASS-42)</p> <p>nerve growth factor (NGF)</p> <p>calcitonin gene-related peptide (CGRP)</p> <p>substance P (SP)</p>	<p>62% of CSU patients reported experiencing at least one stressful life event prior to the onset of urticaria, with a median duration of 3.5 months between the event and onset</p> <p>74% of CSU patients reported that their urticaria symptoms were exacerbated by stress</p>
<p>Ali et al. (2021, Denmark) [69]</p>	<p>85 CSU</p> <p>The Holmes-Rahe Stress Inventory</p> <p>Urticaria Activity Score in the past 7 days (UAS7)</p> <p>Dermatology Life Quality Index (DLQI)</p>	<p>Emotional stress (43.5%), traveling abroad (20.0%), infections (18.8%), new jobs (16.5%), and weight changes (14.1%) were the most frequently reported life events occurring immediately before the onset of CU</p> <p>Patients experiencing emotional stress prior to CU onset were more likely to develop angioedema and tended to have higher UAS7 and DLQI scores</p> <p>Emotional stress was also associated with a tendency to have CINDU and a positive urticaria histamine release (HR) test</p>
<p>Malhotra et al. (2008, India) [70]</p>	<p>50 psoriasis, 50 CU</p> <p>Gurmeet Singh's Presumptive Stressful Life Events (PSLE) scale</p>	<p>26% of patients in the psoriasis group and 16% in the chronic urticaria group reported experiencing stressful life events within one year preceding the onset or exacerbation of their skin disease</p> <p>In the chronic urticaria group, the most common stressful life events were the death of a close family member (6%), family conflict (2%), and financial loss or problems (2%)</p> <p>In the chronic urticaria group, 63.6% of stressful life events occurred within six months and 45.4% within one month preceding the onset or exacerbation</p>

**Table 1** (continued)

Manuscript	Methodology and scales/questionnaires/biomarkers used	Key takeaways
Chung et al. (2010, UK) [71]	100 CIU/60 allergy patients Posttraumatic Stress Diagnostic Scale (PDS) General Health Questionnaire-28 (GHQ-28) Social Readjustment Rating Scale (SRRS) Perceived Stress Scale (PSS) NEO-Five Factor Inventory	34% of CIU patients met the diagnostic criteria for PTSD, compared to 18% of allergy patients CIU patients were 1.89 times more likely to have a current diagnosis of PTSD than the control group The primary traumas included sudden unexpected death of someone close, life-threatening injury or illness, childhood abuse, physical assault in adulthood, and serious accidents CIU patients with PTSD reported higher scores on somatic problems, anxiety, and social dysfunction compared to those without PTSD and allergy patients with and without PTSD PTSD diagnosis and neuroticism were significantly associated with psychiatric comorbidity
Hunkin et al. (2012, UK) [72]	91 CIU patients The study aimed to investigate the interrelationship between chronic idiopathic urticaria (CIU), psychological comorbidity, post-traumatic stress disorder (PTSD) symptoms, defense mechanisms, and alexithymia Posttraumatic Stress Diagnostic Scale (PDS) General Health Questionnaire-28 (GHQ-28) Social Readjustment Rating Scale (SRRS) Perceived Stress Scale (PSS) NEO-Five Factor Inventory (NEO-FFI)	CIU participants reported significantly more life events, PTSD symptoms, perceived stress, and psychological comorbidity than the control group CIU patients were nearly twice as likely to meet the criteria for full PTSD compared to controls PTSD severity was significantly associated with both psychological comorbidity and CIU severity
Studies associating stress levels with urticaria severity Chung et al. (2010, UK) [73]	100 CSU/60 allergy patients Participants are instructed to complete surveys to measure the levels of life event stress, perceived stress, and coping strategies General Health Questionnaire (GHQ) Social Readjustment Rating Scale (SRRS) Perceived Stress Scale (PSS) Ways of Coping Checklist (WCC) 46 CU/33 controls Urticaria Activity Score (UAS 7) Itch Severity Evaluation Questionnaire Visual Analogue Scale (VAS) to measure stress intensity Social Readjustment Rating Scale (SRRS) Chronic Urticaria Quality of Life Questionnaire (CU-QoL)	CSU patients had higher levels of life event stress and perceived stress compared to allergy patients CSU patients exhibited greater psychiatric co-morbidity, characterized by symptoms of somatic issues, anxiety, social dysfunction, and depression Emotion-focused coping strategies were associated with the severity of CIU, while perceived stress was linked to psychiatric co-morbidity CU patients experienced significantly higher stress levels compared to the control group No significant difference in the number of stressful life events between CU patients and controls QoL was significantly impaired in CU patients, with the most affected subscales being itching and embarrassment Disease severity was positively correlated with global itch score, itch intensity, range, and higher stress levels Strong correlations between stress and QoL subscales, especially itching and swelling/mental status
Ograczyk-Piotrowska et al. (2018, Poland) [74]		

Table 1 (continued)

Manuscript	Methodology and scales/questionnaires/biomarkers used	Key takeaways
Schut et al. (2020, Germany) [75]	<p>CSU+ (249 patients): Patients with identified potentially relevant underlying conditions</p> <p>CSU- (54 patients): Patients without identified underlying conditions</p> <p>Urticaria Activity Score (UAS7)</p> <p>Perceived Stress Questionnaire (PSQ)</p> <p>SWOP Questionnaire</p> <p>total serum IgE, blood basophil, and eosinophil counts</p> <p>79 CU/39 asthma patients</p> <p>Hospital Anxiety and Depression Scale (HADS)</p> <p>Stress Response Inventory (SRI)</p> <p>Chronic Urticaria Quality of Life (CU-QoL) Questionnaire</p> <p>Urticaria Activity Score (UAS)</p> <p>Visual Analog Scale (VAS) to assess the severity of pruritus and sleep difficulty</p>	<p>A wide range of stress levels was reported among CSU patients, with 21% experiencing low stress, 64% moderate stress, and 15% high stress</p> <p>A significant link between perceived stress and disease activity was found in CSU- patients, even before they were informed that no underlying cause for their urticaria would be found</p> <p>The findings suggest a possible causal relationship between CSU and mental distress</p> <p>Depression was present in 48.1% of CU patients and 28.2% of asthma patients (<math>p &lt; 0.039</math>)</p> <p>Anxiety was present in 38.0% of CU patients and 41.0% of asthma patients</p> <p>Stress levels tended to be higher in asthma patients, but this was not statistically significant</p> <p>CU patients with anxiety had lower CU-QoL scores, higher pruritus-VAS scores, higher UAS-6 scores, and higher stress levels</p> <p>CU patients with depression had lower serum total immunoglobulin E (IgE) levels and higher stress levels</p> <p>Depression was associated with sleep difficulty</p> <p>Anxiety was associated with pruritus severity and urticaria severity</p> <p>Stress was associated with sleep difficulty, pruritus severity, and urticaria severity</p> <p>Depression was associated with sleep difficulty, anxiety with pruritus severity and urticaria severity, and stress with sleep difficulty, pruritus severity, and urticaria severity</p> <p>Depression and stress scores were significantly higher in CSU patients compared to controls</p> <p>No significant difference in anxiety scores between CSU patients and controls</p> <p>Depression, anxiety, and stress scores were higher in CSU patients with severe disease</p> <p>The study confirmed a high prevalence of depression and stress in CSU patients, with significant differences compared to healthy controls</p> <p>Women are more susceptible to depression, anxiety, and stress than men in the context of CSU</p> <p>Over half of the CSU patients experienced moderate to severe impairment in QoL and stress</p> <p>Disease severity and the presence of angioedema significantly impacted QoL and stress levels</p>
Choi et al. (2020, Korea) [22]		
Rani et al. (2022, India) [76]	<p>125 CSU/40 healthy control</p> <p>Urticaria Activity Score (UAS)</p> <p>Depression Anxiety Stress Scale (DASS-21)</p>	
Reeshma et al. (2024, India) [77]	<p>54 CSU</p> <p>Urticaria Activity Score (UAS-7)</p> <p>Chronic Urticaria-Quality of Life (CU-QoL) Questionnaire</p> <p>Perceived Stress Scale (PSS)</p>	

**Table 1** (continued)

Manuscript	Methodology and scales/questionnaires/biomarkers used	Key takeaways
Badura-Brzoza et al. (2021, Poland) [78]	71 CSU Urticaria Activity Score (UAST) State-Trait Anxiety Inventory (STAI) Sense of coherence SOC-29 questionnaire	Patients with chronic spontaneous urticaria (CSU) who also suffer from angioedema exhibit lower sense of coherence (SOC) compared to patients with CSU who only experience wheals  Lower SOC is associated with higher anxiety levels in these patients  Presence of angioedema in CSU patients exacerbates the psychological burden of the disease, leading to a more pronounced impairment in SOC and increased susceptibility to anxiety
Tawil et al. (2023, Lebanon) [23]	295 CU patients Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) Dermatology Life Quality Index (DLQI) Patient Health Questionnaire-9 (PHQ-9) Beirut Distress Score 22 (BDS-22) Urticaria Control Test (UCT)	Patients with poorly controlled CU had higher PHQ-9 and BDS-22 scores, indicating higher levels of psychological distress and depression  Emotional stress and spontaneous type of urticaria were associated with higher CU-Q2oL scores  CU significantly impairs patients' quality of life and psychological well-being, with more severe disease correlating with greater psychological distress
Studies that suggest the role of chronic stress in the development and exacerbation of chronic urticaria		
Varghese et al (2016, India) [63]	45 CU/45 controls The primary aim was to explore the associations between these biomarkers, stress levels, and CU severity  Urticaria Activity Score (UAS) Presumptive Stressful Life Events (PSLE) scale Daily Hassles and Uplifts Scale-Revised (DHUS-R) Inflammatory markers such as C-reactive protein (CRP) and interleukin-18 (IL-18) were measured using enzyme-linked immunosorbent assay kits. Cortisol levels were assessed using chemiluminescence.	The study found significantly higher levels of systemic inflammation markers (hs-CRP and IL-18) and stress scores (PSLE and DHUS-R) in CU patients compared to controls  There was a marked reduction in basal cortisol levels in CU patients, which was more pronounced with increasing disease severity and in cases of autoimmune urticaria. Hypocortisolism was significantly associated with higher levels of hs-CRP, IL-18, PSLE, and DHUS-R scores, as well as with the duration and severity of urticaria symptoms  The findings suggest a significant role of chronic stress in the pathogenesis of CU, contributing to a vicious cycle of inflammation and hypocortisolism
Dyke et al. (2008, UK) [64]	30 CIU/30 controls Basophil activation test Serum cortisol, CRF, ACTH	Higher serum cortisol concentrations in CIU patients, although this was not statistically significant  CIU patients exhibited heightened basophil response to CRF and ACTH, suggesting hyperresponsiveness  The lack of correlation between cortisol levels and basophil activation in CIU patients suggests a disruption in the normal feedback mechanisms of the HPA axis  The findings support the notion that stress and HPA axis dysregulation play a role in the pathophysiology of the disease

Table 1 (continued)

Manuscript	Methodology and scales/questionnaires/biomarkers used	Key takeaways
Papadopoulou et al. (2005, USA) [79]	3 CU, 5 control Skin biopsies CRH receptor-1 (CRH-R1) histidine decarboxylase (HDC)	CRH-R1 mRNA expression was significantly higher in chronic urticaria patients compared to normal foreskin and unaffected breast skin The highest expression levels of CRH-R1 and HDC were found in patients who reported that their symptoms worsened with emotional stress This supports the hypothesis that stress exacerbates CU through the activation of CRH-R1 and subsequent mast cell degranulation
Studies suggesting potential health risks caused by the chronic stress in CU	34 CSU/28 controls Heart rate variability (HRV) baroreflex sensitivity (BRS) inflammatory markers (s-cortisol, IL-6, IL-18, hs-CRP), Perceived Stress Scale Pittsburgh Sleep Quality Index	CSU patients exhibit cardiac dysautonomia characterized by increased sympathetic and decreased parasympathetic activity These patients also show higher levels of perceived stress and inflammation, and poorer sleep quality, potentially increasing their cardiovascular morbidity and mortality risk Regular screening of cardiovascular health in CSU patients is recommended to mitigate these risks
Ferdous et al. (2023, India) [80]		

stressful events before disease onset, with an average of 2.3 events per patient) [83]. Additional studies found that effective coping mechanisms and family support reduce CU risk [67]. Common stressors include the loss of family members, financial difficulties, family conflict, and work issues [70]. Recent research indicates that stress precedes CU exacerbation in a significant portion of patients, with many recalling stress events months before disease onset [68, 84].

### Role of neuronal molecules in chronic urticaria

As previously mentioned, neuronal molecules including neuropeptides and neurotransmitters play a crucial role in the pathophysiology of CU. These molecules are produced and released by neurons or MCs, contributing to neurogenic inflammation and pruritus in CU.

Several studies have consistently highlighted the role of SP in CU. SP is a neuropeptide involved in neurogenic inflammation, it binds to neurokinin-1 receptors (NK1R) or MRGPRX2 on MCs, leading to the release of histamines and other pro-inflammatory mediators, resulting in itch, wheals and/or angioedema [85]. The number and proportion of MRGPRX2-positive MCs are significantly higher in the skin of CU patients compared to healthy controls [60], which suggests that CU patients may be more susceptible to the effects of SP, leading to increased MCs activation and subsequent histamine release. SP levels are notably higher in CU patients compared to healthy controls and positively correlate with urticaria severity and in some studies increased in CSU patients with comorbid depression [65, 86–88]. These indicate SP's role in modulating the inflammatory response and exacerbating urticaria symptoms. SP also stimulates basophils expressing NK-1R, leading to stronger inflammatory responses [87]. Furthermore, SP is a key mediator in neurogenic inflammation, linking the nervous system and immune response in the skin [89], and might act as a trigger in CU [90, 91]. The ability of SP to activate MCs is concentration dependent [92]. A human skin microdialysis study demonstrated that SP could induce histamine release from MCs only at high concentrations [92]. Calcitonin Gene-Related Peptide (CGRP) is another neuropeptide that contributes to vasodilation and increased vascular permeability, which are hallmark features of urticarial lesions [93]. In patients with CU, the number of CGRP-positive cells is increased in lesional skin, while non-lesional skin shows CGRP expression levels similar to healthy controls [93]. This finding indicates that CGRP released from sensory nerves can amplify the inflammatory response in CU by interacting with its receptors on MCs and other immune cells, contributing to the pathogenesis of the disease. The increased expression of corticotropin-releasing hormone receptor 1 (CRH-R1) in CU lesions also suggests a close connection between the skin and the HPA axis [79]. In addition, some studies have not observed elevated levels of

**Table 2** Studies evaluating the neuronal molecules in CU

Study	Population	Results
Elçin et al. (2024, Turkey) [68]	42 CSU vs. 42 HC	Patients with CSU who benefited from omalizumab had similar psychological status as healthy controls. Serum NGF levels were lower and CGRP levels were higher in CSU patients
Boyvadoglu et al. (2023, Turkey) [94]	30 CSU vs. 20 HC	After treatment with omalizumab, serum SP and CGRP levels increased, IL-31 levels decreased, no change in NPY levels
Memet et al. (2021, Turkey) [88]	60 CU (30 with depression, 30 without) vs. 30 HC	Serum SP levels were significantly higher in CU patients with depression than in those without depression. Urticaria disease activity and severity of depression were positively linked
Zheng et al. (2016, China) [87]	15 CU vs. 15 HC	SP levels were higher in CU patients than in HC. Targeting SP/NK1R system could potentially be effective
Basak et al. (2014, Turkey) [65]	57 CU vs. 46 HC	In this study, SP, SCF, and NPY were found to play a role in CU. NPY was the most significant predictor of APST positivity, indicating its role in CU autoimmunity
Metz et al. (2014, Germany) [86]	118 CU vs. 30 HC	CU patients have increased SP levels, correlating with disease severity
Basak et al. (2014, Turkey) [65]	38 CU vs. none	H1-antihistamines have an impact on the serum concentrations of neuropeptides, reducing NPY, VIP, SCF, and NGF, but elevating CGRP
Rossing et al. (2011, Germany) [66]	50 CU vs. 23 HC	Elevated BDNF levels were found in both the serum and the skin lesions of CU patients
Dyke et al. (2008, UK) [64]	30 CU vs. 30 HC	While both CRF and ACTH were demonstrated to activate basophils, no significant difference was observed in the response rates of CU patients and HC. However, CU patients exhibited elevated serum cortisol levels, suggesting dysregulation of the HPA axis
Ozseker et al. (2008, Turkey) [97]	42 CU vs. 22 HC	Baseline NGF levels were lower in CU non-responder compared to responder and HC. NGF levels increased in CU responder following symptom suppression
Tedeschi et al. (2005, Italy) [98]	117 CU (40 with atopy), 24 HC	SP might serve as a trigger for urticaria in a subset of CU patients
Borici-Mazi et al. (1999, Canada) [99]	18 CU (including 9 CInDU) vs. 9 HC	CU patients exhibited enhanced wheal and flare responses to SP and CGRP. While H1-antihistamines partially inhibited both SP-induced wheal and flare reactions, they more effectively suppressed CGRP-induced flare, particularly in CU patients
Heyer et al. (1998, Germany) [100]	16 CU vs. 16HC	CU patients demonstrated a reduced axon-reflex erythema following histamine iontophoresis, suggesting decreased C-fiber responsiveness to histamine
Georgala et al. (1994, Greece) [101]	14 CU vs. 15 HC	CU patients exhibited elevated mean b-endorphin levels compared to HC, suggesting heightened opioid system activation in CU
Smith at el (1992, UK) [102]	10 CU vs. 10 HC	CU patients exhibited a pronounced increase in VIP-induced wheal formation, suggesting heightened sensitivity of the VIP microvasculature in this CU subset

SP and CGRP in the circulation of urticaria patients, these contradictory findings also exist for other neuropeptides and neurotransmitters, including stem cell factor, nerve growth factor, vasoactive intestinal peptide, neuropeptide Y, vasoactive intestinal peptide, corticotrophin-releasing hormone, adrenocorticotrophic hormone, cortisol, dehydroepiandrosteron-sulfat,  $\beta$ -endorphin, and histamine [65] (Table 2). We speculate that this may be due to several reasons [94, 95]: a. some molecules, such as SP, may degrade rapidly in the blood, affecting detection. b. a single or several molecules are not the sole mediators of CU pathophysiology. c. these

molecules may be present in affected tissues (such as X2-positive cells, CGPR-positive cells, and CRH-1R-positive cells in urticarial lesions) rather than in the circulation. A significant portion of these molecules or receptors, in addition to being expressed in the brain, can also be expressed by the skin itself, as we know that stress, can be both a cause and a consequence of the disease [5, 79, 85, 93]. Therefore, successful research on these molecules and their receptors may lead to more precise treatment strategies, ultimately changing the prognosis for CU patients and open horizons for new treatment targets [96].

## Management and future directions in CU

### Psychopharmacological interventions

As mentioned previously, the pathophysiology of CSU involves neuro-immune interactions, with psychological stress acting as a triggering and modulating factor in the disease course, suggesting the potential benefits of psychiatric treatments and non-invasive interventions to reduce stress and anxiety in CSU patients [85]. Studies emphasize the importance of a multidisciplinary approach, incorporating psychological interventions alongside traditional pharmacotherapy for CSU [85, 103]. Furthermore, psychotropic medications have shown promise in treating refractory chronic idiopathic urticaria (CIU), especially in cases with concurrent psychiatric comorbidity, offering alternative treatment options for challenging cases [104]. Specifically, Mashiro et al. [105] found that long-term combination therapy with psychotropics (including alprazolam) is effective in suppressing urticaria for patients who had high scores in psychometric evaluations and moderately effective for those with a low score in these areas. In two randomized, double-blind, placebo-controlled studies where a potent opiate antagonist Nalmefene was evaluated in 80 patients with severe pruritus caused by CU (21 subjects) and by atopic dermatitis (59 subjects), the itch that was evaluated after 6 h of drug intake diminished by 60% in patients taking 10 mg of nalmefene and 35% in patients taking 20 mg of nalmefene. The responses were similar in CU and AD patients however, 67% of patients experienced adverse effects including dizziness, fatigue, and nausea [106]. Despite the well-documented suppressive effect of tricyclic antidepressants on histamine-induced wheal-and-flare reactions [107], there have been few reports on the efficacy of incorporating antidepressants into the treatment regimen for chronic urticaria. In few case reports, mirtazapine, fluoxetine and sertraline was found to be effective in controlling or decreasing the symptoms of urticaria which was accompanied by psychiatric disorders such as anxiety, depression and panic disorder [108–110]. Beyond the purely psychiatric treatments, doxepin, a tricyclic antidepressant which has H1- and H2-antihistaminic and anticholinergic properties has been shown to be effective in the treatment of CSU dosed at 10–25 mg three times daily [111]. In a more recent study from Turkey [112], doxepin was effective in 75% of difficult to treat 36 CSU patients where 44.4% showed a complete response. Mild sedative and anticholinergic side effects were well tolerated by the patients.

### Psychotherapeutic interventions

The role of psychotherapy in the management of CU has only been studied in case reports. Gupta et al. reports of 5 CSU cases with post-traumatic stress disorders whose urticaria

symptoms resolved after psychiatric treatment including psychotherapy [113], while Vojvodic et al. reported a case of CSU with generalized anxiety disorders whose urticaria flares decreased after psychotherapy [103]. Mind-body approaches have gained attention as complementary strategies in managing chronic urticaria (CU), focusing on reducing stress and improving overall well-being. Ridge et al. [114] evaluated the feasibility of an 8-week attention-based training (ABT) program, coupled to biofeedback technology in 12 CSU patients. They reported a decrease in severity of urticaria symptomatology as measured by the urticaria control test upon completion of the intervention. Tull et al. [115] reported the results of a one-session behavioral activation treatment for depression designed for 11 CSU patients with chronic, poorly controlled urticaria and symptoms of depression. One month after the intervention, participants exhibited significant reductions in depression severity, avoidance/rumination, and work/school impairment with improvements in urticaria control. Shertzer et al. [116] reported six patients were free of hives and an additional seven reported improvement of their urticaria after been treated with hypnosis with relaxation therapy in 15 CU patients.

### Future possible targets

As mentioned above, neuromediators such as SP and CGRP as well as MRGPRX2 receptors are involved in the neurogenic inflammation in CU. Therefore, targeting neurogenic inflammation can be a promising approach for developing future treatments for CU. For this aim, one approach could be using neuropeptide antagonists such as aprepitant, serlopitant and tradipitant which are a neurokinin-1 receptor (NK1R) antagonists [117, 118], while CGRP inhibitors such as fremanezumab and galcanezumab could be other options (ref). On the other hand, since CRH is involved in the stress response and can induce mast cell degranulation and found to be increased in CU [79], Antalarmin, a CRH receptor antagonist, could be evaluated especially for patients who have CU exacerbated by stress. However, among these molecules, the most intriguing one are the MRGPRX2 antagonists. Blocking MRGPRX2 can effectively mitigate the effects of neuromediators like substance P and CGRP in CU by preventing the activation of mast cells and the subsequent inflammatory cascade. There are currently ongoing clinical trials that are evaluating the efficacy of EVO756 and EP262 which are potent MRGPRX2 antagonists in CSU and CIndU [119].

## Conclusion

The comprehensive management of chronic urticaria (CU) necessitates a holistic, whole-body approach that integrates the understanding of stress levels and psychological factors into the

**Table 3** Self-reported and objective measures to evaluate stress

Measure (Self-report)	Captures (Self-report)	Measure (Objective)	Captures (Objective)
Positive and Negative Affect Schedule (PANAS)	Emotional state during	Heart rate variability	Momentary ANS function
Depression Anxiety and Stress Scale	Negative emotional symptoms	Pulse (heart rate)	Momentary ANS function
Stress Overload Scale (SOS)	Stress overwhelming coping mechanisms	Electrodermal activity (EDA)	Momentary ANS function
Hassles and Uplifts Scale	Distressing demands	Blood pressure	Momentary ANS function
Perceived Stress Scale (PSS)	The view of the person as their life as uncontrollable	Blood epinephrine and norepinephrine	Acute ANS function
Standard Stress Scale	Generalized view on life stress	Electromyographic activity	Tension—muscle activity
Trier Inventory for Chronic Stress (TICS)	Chronic psychological stress	Salivary alpha-amylase	Acute ANS function
Impact of Event Scale	Distress linked to a specific event	Salivary and blood cortisol	Acute HPA axis function
Stress Appraisal Measure	Appraisal of an anticipated, specific stressor	Urine cortisol	Short-term HPA axis function
Perceived Stress Questionnaire	Cognitive perceptions of stress	Urine epinephrine and norepinephrine	Short-term ANS function
Life Events Checklist	Stressful events over the life course	Hair cortisol	Chronic HPA axis Function
Life Events and Difficulties Schedule (LEDS)	Major environmental stress exposures and subjective reactions		

treatment regimen. Studies have consistently shown that stress and psychological trauma are significant predisposing factors in the development and exacerbation of CU. Elevated stress levels and poor coping mechanisms not only trigger urticaria flare-ups but also contribute to the chronicity and severity of the disease.

Healthcare providers should prioritize the psychological well-being of CU patients by incorporating strategies to mitigate stress and providing supportive, empathetic care. This includes regular psychological assessments using validated tools such as the Perceived Stress Scale (PSS), Depression Anxiety Stress Scale (DASS-21), and the Patient Health Questionnaire-9 (PHQ-9). Other measures that are suggested to be used in the evaluation of patients' stress levels in clinical practice or clinical studies are provided in Table 3.

Moreover, adopting a patient-centered approach that involves clear communication, active listening, and providing reassurance can significantly improve patient outcomes. Educating patients about the potential impact of stress on their condition and equipping them with effective stress management techniques, such as mindfulness, cognitive-behavioral therapy, and relaxation exercises, can help reduce the psychological burden associated with CU.

Integrating mental health support, including referrals to mental health professionals when necessary, is crucial for patients exhibiting significant psychological distress or comorbid conditions like depression, anxiety, or PTSD. By addressing both the physical and psychological aspects of CU, healthcare providers can enhance the quality of life for patients, promoting better disease control and overall well-being. This multidimensional approach underscores the necessity for a collaborative effort

between dermatologists, allergists, and mental health professionals to ensure comprehensive care for CU patients.

However, in light of the evidence presented, it is important to exercise caution when interpreting the relationship between psychological stress and CSU. While multiple studies suggest a potential link, the data are not yet robust enough to confirm whether this connection is due to shared pathophysiological mechanisms or a coincidental association. Furthermore, retrospective studies are prone to memory bias, and the molecular mechanisms identified between stress and urticaria are also observed in other chronic inflammatory conditions. Finally, the small sample sizes and lack of blinded evaluations in pharmacological studies suggest the need for further, more rigorous research before definitive conclusions can be drawn. Future studies should aim to better delineate the directionality of this relationship and include more objective measures of disease activity and should continue to explore the complex interactions between stress, neuroimmune pathways, and CU to develop targeted therapies that address these interconnections effectively.

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**Conflict of Interest** MT has no relevant conflict of interest in relation to this work. Outside of it, MT is or recently was a speaker and/or advisor for Novartis, AstraZeneca, GSK, Vem İlaç, Polifarma. EK is or recently was a speaker and/or advisor for Novartis, Menarini, LaRoche Posey, Sanofi, Bayer, outside the submitted work. The rest of the authors declare no conflict of interest.

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