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The Skin-Brain Axis' Role in Acne: A Mechanistic Synthesis Review

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Abstract

Acne vulgaris is a prevalent and chronic inflammatory skin disorder that involves complex interactions among the neuroendocrine, immune, sebaceous, and microbial systems. Emerging evidence suggests that the body's physiological stress response contributes to acne severity by modulating inflammatory and sebaceous pathways. This review synthesizes current literature examining the relationship between these physiological stress responses and acne pathogenesis.

The skin expresses functions of its own hypothalamic-pituitary-adrenal (HPA)-like axis that is capable of responding to stress signals. In the neuroendocrine system, corticotropin-releasing hormone (CRH) and other stress-related mediators stimulate sebocyte lipid synthesis and inflammatory activity within the pilosebaceous unit of the skin. In the immune system, evidence from literature shows that *Cutibacterium acnes* (the bacteria associated with acne vulgaris) also activates innate immune signaling pathways, causing inflammatory cytokine production and lesion development. Elevated levels of Substance P have additionally been associated with increased acne severity, sebocyte activation, mast cell activation, and enhanced inflammatory responses.

Collectively, current evidence supports a neuroendocrine-immune model of acne pathogenesis in which stress signaling and responses contribute to inflammatory amplification and sebaceous gland dysregulation. These findings highlight potential therapeutic targets involving neuroendocrine and neuroimmune pathways in treating acne vulgaris.

Keywords

Skin–Brain Axis'; Mechanistic Synthesis; Chronic inflammatory skin; Neuroendocrine; Immune; Sebaceous; Microbial systems.

Introduction

Acne vulgaris is a chronic inflammatory condition that originates from the pilosebaceous unit of the skin [1], with a major characteristic being the proliferation of *Cutibacterium acnes (C. acnes)* bacteria [2]. It is one of the most prevalent dermatological conditions worldwide, affecting persons of all ages, and is influenced by both systemic and environmental factors [3]. The pathogenesis of acne has been established as multifactorial, and includes increased sebum production, disordered follicular keratinization, microbial colonization, and immune dysregulation [1,4]. This manifests as lesions ranging from blackheads and whiteheads to pimples (papules and pustules), cysts, and nodules, which commonly appear on the face, neck, back, and chest.

Anecdotally but widely, there has been an observed association between stress and acne exacerbation. Across clinical and experimental studies, there has been a consistent observation of exposure to stress being associated with acne severity [5,6], however the intricacies remain complex and largely misunderstood. There seems to be a bidirectional nature to this relationship, as while the onset of the body's physiological stress response to stress may be positively correlated to the increased severity of acne [7], the increasing severity of acne itself can act as a stressor that then further exacerbates the existing symptoms. Though this observation exists, the exact mechanistic pathways by which this plays out have not been fully integrated.

To approach this, it is important to establish a relationship between how the body chemically reacts to external stressors and the pathogenesis of acne. Real or perceived physiological stress activates the neuroendocrine response of the synergistically acting sympathetic nervous system and central hypothalamic-pituitary-adrenal (HPA) axis [5,8], which mediates stress responses to maintain homeostasis [9]. The activation of the HPA axis results in the release of corticotropin-releasing hormone (CRH) from the hypothalamus [5,8], which then stimulates the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH), which travels to the adrenal gland and results in the production of cortisol [5,9]. These signals are matched in the skin, where local production of CRH and neuropeptide release affect sebocyte activity and immune cell function.

The activation of stress-related neuroendocrine pathways promotes increased lipid synthesis and inflammatory signaling within the pilosebaceous unit. Corticotropin-releasing hormone (CRH) has been shown to directly increase sebocyte lipid production, while inflammatory mediators IL-1β, IL-6, and TNF-α are upregulated in response to microbial and immune activation [2,4,10,11]. Sustained activation of these pathways has been associated with chronic low-grade inflammation in stress-related conditions, reflecting prolonged dysregulation of the hypothalamic–pituitary–adrenal axis and immune signaling [5,9].

Physiological stress responses can be quantified using systemic biomarkers such as serum or salivary cortisol and catecholamines, as well as cutaneous markers including CRH receptor expression and neuropeptide levels such as Substance P [6,7,12].

Acne develops within a pre-existing biological framework in which the skin microbiome, particularly *Cutibacterium acnes*, represents a consistent component. However, the presence of *C. acnes* alone is

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insufficient to induce disease, and variations in host immune responses are critical determinants of lesion formation [1,2]. Immune pathways involving cytokine signaling and IL-17–associated responses further contribute to inflammatory amplification within lesions [4,13].

In this context, physiological stress is best understood as a modulator of host–microbe and neuroimmune interactions rather than a primary initiator of acne. While existing literature has characterized individual components of acne pathogenesis and stress-related signaling, there remains a lack of integrated mechanistic synthesis connecting stress-induced neuroendocrine pathways with established models of acne development [1,3,14].

There is emergent evidence that supports the idea of skin being a peripheral neuroendocrine organ capable of responding to systemic stress signals through a close relationship to the central endocrine stress axes [14]. The skin's function expresses elements of the hypothalamic-pituitary-adrenal (HPA) axis, including corticotropin-releasing hormone (CRH) and its receptors [10], which is the body's response to stress in efforts to maintain homeostasis, and has the ability to produce neuropeptides such as substance P [15]. These signaling molecules regulate sebaceous gland activity, inflammatory responses, and immune function, establishing a functional skin–brain axis that links systemic physiological stress to a cascade of localized cutaneous responses.

This review evaluates the hypothesis that chronic real or perceived physiological stress exacerbates acne vulgaris through activation of the cutaneous neuroendocrine system, involving CRH signaling, neuropeptide-mediated inflammation, mast cell activation, sebaceous gland dysregulation, and downstream immune modulation within the pilosebaceous unit.

Methods

In February 2026, a targeted literature search of Google Scholar and PubMed was conducted to identify relevant studies and papers on acne vulgaris, associated inflammatory and neuroendocrine mechanisms, and stress-related mechanisms. The search strategy employed combinations of the terms: "acne vulgaris," "stress," "cutaneous HPA axis," "corticotropin-releasing hormone," "CRH," "sebaceous gland," "substance P," "mast cells," "neurogenic inflammation," "skin–brain axis," and "*Cutibacterium acnes*". Additional terms such as "cortisol," "catecholamines," and "pro-inflammatory cytokines" were used to identify studies assessing physiological stress and inflammatory signaling.

The results from the search were filtered by the year of publication, with papers published between 2000 and 2026 meeting the criteria, title and abstract for relevance, followed by reviewing the full text. Studies were considered relevant if they included investigation of mechanistic pathways that connect physiological stress, neuroendocrine processes, immune responses or microbial activity to acne vulgaris or cutaneous inflammation. Any primary research studies involving human subjects, animal models, or in vitro systems were prioritized.

Studies focusing exclusively on psychological or behavioral outcomes without physiological or mechanistic data were excluded. Additional exclusion criteria included studies that were not relevant to acne or inflammation.

Selected studies were qualitatively screened to identify recurring biological mechanisms, such as inflammatory signaling, sebaceous gland activity, neuropeptide involvement, and any cutaneous neuroendocrine regulation. The selected papers were combined to construct an integrated model of the acne pathogenesis and its relationship to physiological processes triggered by stress.

Results

Evidence shows that inflammatory activity is seen in both early acne lesions and skin deemed as clinically unaffected. There is an increased expression of interleukin-1 (IL-1) and other pro-inflammatory mediators seen in early stages of lesion development [4]. This is associated with follicular changes such as hyper keratinization and comedone formation [1]. Inflammatory cell infiltration, including CD4+ T cells and macrophages, is also observed in early acne lesions [4].

Cutibacterium acnes (the bacteria that is associated with acne) activates innate immune responses through Toll-like receptor 2 (TLR2) signaling in keratinocytes and immune cells. This activation induces downstream inflammatory pathways, including NF-κB signaling, resulting in increased production of cytokines such as IL-6, IL-8, IL-12 [2,4], and TNF-α. Differences in inflammatory potential between bacterial strains have been observed, with acne-associated strains producing stronger immune activation [2].

Sebum composition is altered in acne, with increased levels of lipids including squalene, triglycerides, and monounsaturated fatty acids. These lipid changes contribute to follicular hyperkeratinization, promote *Cutibacterium acnes* proliferation, and enhance inflammatory signaling within the pilosebaceous unit [16].

In vitro studies demonstrate that CRH directly stimulates sebocyte activity [10]. CRH exposure increases lipid synthesis in a dose-dependent manner and results in intracellular lipid accumulation [10]. CRH also upregulates steroidogenic enzyme activity, including 3β-hydroxysteroid dehydrogenase, indicating local regulation of sebaceous gland metabolism [3,10,11] (see Figure 1).

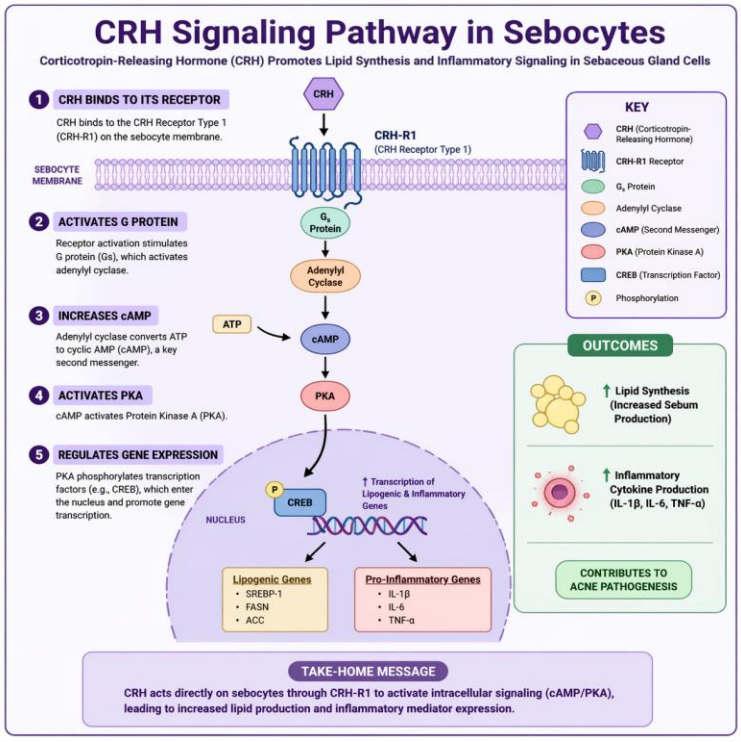

Figure 1: Corticotropin-Releasing Hormone (CRH) Signaling Pathway in Sebocytes.

Corticotropin-releasing hormone (CRH) binds to CRH receptor 1 (CRH-R1) expressed on sebocytes within the sebaceous gland. The binding activates this receptor. This stimulates signaling pathways within the cell that increase lipid synthesis and sebaceous gland activity. CRH signaling also upregulates steroidogenic enzymes, contributing to local androgen metabolism and further enhancement of lipid production. Increased sebaceous activity promotes elevated sebum secretion within the pilosebaceous unit. Altered sebum composition and accumulation then result in follicular hyperkeratinization, microbial proliferation, and inflammatory signaling associated with acne pathogenesis. [10,11,16]. Figure was created using OpenAI ChatGPT image-generation tools according to scientific direction and input provided by the author.

The skin's physiology is not limited to being a barrier, but is also a neuroendocrine organ capable of independently responding to stress, without delegating to the brain. Evidence demonstrates that within the epidermis and pilosebaceous unit, there is an active and localized axis expressed that mimics the central HPA axis, including the production of CRH, ACTH, and steroids akin to cortisol [6,14] (see Figure 2). There are cutaneous cells expressing CRH, CRH receptors, and proopiomelanocortin (POMC), and there is downstream production of ACTH, α-MSH, and β-endorphin [6]. There is also support for enzymes, such as CYP11A1, that are necessary for the synthesis of glucocorticoids, like cortisol [6,14]. Exposure of keratinocytes to *Cutibacterium acnes* extracts induces CRH expression, indicating the response of cutaneous neuroendocrine signaling to microbial stimuli [17]. These pathways operate through autocrine and paracrine mechanisms within the skin [6].

Human studies consistently demonstrate a positive correlation between stress and acne severity [3]. Increased stress scores correlate with higher lesion counts and greater clinical severity [3,18]. Statistical significance has been reported in multiple studies ($p < 0.05$) [3,7,18]. Higher stress levels are also

associated with increased sebum excretion rates in adolescent populations [7].

Patients with acne exhibit elevated serum levels of Substance P when compared to with controls [12,15]. Substance P levels show positive correlations with acne severity and psychological stress scores [12]. Mechanistically, Substance P stimulates sebocyte proliferation, increases lipid synthesis, and activates mast cells [11,19], contributing to inflammatory responses in the skin (see Figure 2).

Experimental evidence demonstrates that Substance P modifies cutaneous microbial behavior. Exposure of *Cutibacterium acnes* to Substance P increases bacterial virulence and inflammatory potential, also contributing to enhanced inflammatory responses in the skin [20] (see Figure 2).

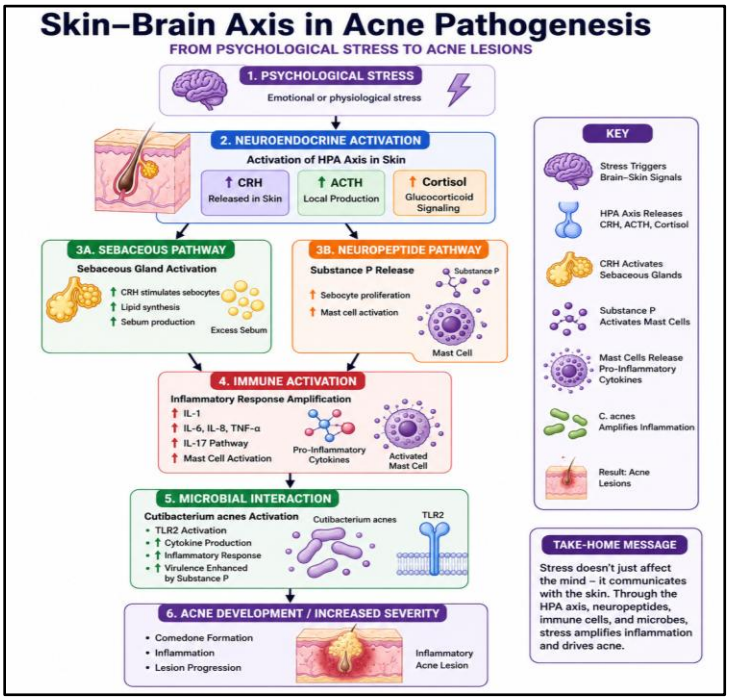

Figure 2: Integrated Neuroendocrine–Immune Model of the Skin–Brain Axis in Acne Pathogenesis - A Synthesis Model.

Psychological stress activates the hypothalamic-pituitary-adrenal (HPA)-like axis within the skin, which results in increased production of including corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol. This activates sebaceous glands by increasing sebocyte lipid synthesis and sebum production within the pilosebaceous unit. Simultaneously, stress-induced neuropeptide signaling causes the release of Substance P, which stimulates sebocyte proliferation and activates mast cells within the skin. These events contribute to amplifying inflammatory signaling by releasing pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor-α (TNF-α), and activating IL-17–associated immune pathways. These lead to follicular hyperkeratinization and lesion progression. *Cutibacterium acnes* further increases inflammation by activating Toll-like receptor 2 (TLR2)-mediated signaling pathways, resulting in even more increased cytokine production and additional recruitment of inflammatory cells. Exposure to Substance P additionally increases the inflammatory potential of *Cutibacterium acnes*, further enhancing host inflammatory responses. Collectively, these mechanisms contribute to the development and severity of acne including comedone formation, inflammatory lesion development, and progression of acne pathology. [2,10,11,13,14,15,17,19].

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Figure was created using OpenAI ChatGPT image-generation tools according to scientific direction and input provided by the author.

Immunological analyses of acne lesions demonstrate increased mast cell density and activation of IL-17–associated immune pathways in early-stage disease [13]. Mast cells contribute to IL-17 signaling and inflammatory amplification in acne lesions, indicating involvement of both innate and adaptive immune responses. [13,19].

Animal model studies demonstrate that psychological stress induces cutaneous inflammation through pathways dependent on Substance P. Stress exposure increases Substance P release and inflammatory cell infiltration, while pharmacological inhibition of Substance P reduces inflammatory responses [21].

Discussion

The findings of this review-based synthesis support a framework in which acne vulgaris is driven by the interaction of a number of systems, namely inflammatory, microbial, sebaceous, immune, and neuroendocrine. Across the included studies, there is consistency in the idea that inflammatory signaling is present early in lesion development and is closely linked with both microbial activation and sebaceous gland dysfunction [1,4].

A key observation across studies is that inflammation is not merely a secondary consequence of comedone formation but is instead present in early and even clinically unaffected skin. The identification of increased interleukin-1 signaling and immune cell infiltration in early lesions suggests that immune activation is an initiating or early amplifying event in acne pathogenesis. This aligns with findings showing that follicular hyperkeratinization and comedone formation are closely associated with inflammatory cytokine activity [4].

Microbial involvement, particularly through *Cutibacterium acnes*, further contributes to this inflammatory environment. Activation of Toll-like receptor 2 and downstream NF-κB signaling pathways results in the production of pro-inflammatory cytokines, including IL-6, IL-8, IL-12, and TNF-α [2]. Importantly, differences in inflammatory potential between bacterial strains suggest that acne is not solely determined by bacterial presence, but rather by host–microbe immune interactions.

Sebaceous gland activity represents a central functional node within this system. Alterations in sebum lipid composition contribute to both microbial proliferation and inflammatory signaling, while also promoting keratinocyte hyperproliferation [16]. These findings indicate that sebaceous glands are not passive targets but active contributors to inflammatory amplification within the pilosebaceous unit.

A major integrative finding across studies is the role of neuroendocrine signaling in regulating sebaceous and inflammatory processes. Corticotropin-releasing hormone (CRH) has been shown to directly increase sebocyte lipid synthesis in a dose-dependent manner and to upregulate steroidogenic enzyme activity [10]. In parallel, skin cells express functional components of a hypothalamic–pituitary–adrenal (HPA)-like axis, including CRH, POMC, and ACTH, indicating that the skin is capable of autonomous neuroendocrine signaling [14]. Notably, microbial stimuli such as *Cutibacterium acnes* extracts can induce CRH expression

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in keratinocytes [17], suggesting bidirectional communication between microbial and neuroendocrine systems. This supports a model in which environmental and microbial stressors may amplify local neuroendocrine responses that contribute to sebaceous activation and inflammation.

The body's stress response emerges as a consistent clinical correlate of acne severity. Across human studies, higher stress levels are associated with increased lesion counts, higher clinical severity scores, and increased sebum excretion [7,18]. These associations are further supported by neuropeptide findings, particularly Substance P, which is elevated in acne patients and correlates with both stress and disease severity [15].

Mechanistically, Substance P has been shown to stimulate sebocyte proliferation, enhance lipid synthesis, and activate mast cells, thereby linking stress-related signaling to both sebaceous and immune pathways [11,19]. Experimental evidence further indicates that Substance P can modify *Cutibacterium acnes* behavior, increasing its inflammatory potential [20]. Together, these findings suggest that stress-associated neuropeptides may serve as key intermediaries between psychological stimuli and cutaneous inflammation.

Immune amplification through mast cell activation and IL-17–associated pathways further contribute to disease progression. The presence of mast cells and IL-17–producing cells in early acne lesions indicates that both innate and adaptive immune responses are engaged early in disease development [13]. In animal models, stress exposure has been shown to induce neurogenic inflammation via Substance P–dependent mechanisms, further supporting a causal role for neuropeptide signaling in inflammatory amplification [21].

Collectively, the included studies support a multi-system model of acne pathogenesis in which microbial activation (*C. acnes*), sebaceous gland dysfunction, innate and adaptive immune responses, neuroendocrine signaling (CRH, Substance P), and psychological stress are interconnected rather than independent processes. The evidence suggests that acne should be understood as a systems-level disorder involving continuous bidirectional communication between the skin, immune system, and neuroendocrine pathways.

Future implications and applications

The findings of this synthesis highlight several potential directions for future research and clinical application.

Despite strong mechanistic and hypothetical support and the ability to trace this pathway, there is a high level of variability in stress quantification and reliance on animal models. This highlights the need for standardized, human-based studies to be added to the body of knowledge. Targeting neuroendocrine and neuroimmune pathways represents a promising direction for future therapeutic development.

The role of neuroendocrine signaling suggests that therapeutic strategies targeting stress-related mediators such as CRH or Substance P may represent approaches for the treatment of acne vulgaris. The modulation of these pathways could potentially reduce sebaceous gland activation and inflammatory

signaling simultaneously.

The identification of immune involvement in early lesion formation suggests that early intervention targeting inflammatory mediators such as IL-1 or IL-17 may be more effective than treatments focused solely on bacterial reduction or sebum suppression.

The bidirectional relationship between *Cutibacterium acnes* and host neuroendocrine signaling suggests that future therapies may need to address both microbial composition and host immune responsiveness rather than focusing exclusively on antimicrobial approaches.

Finally, the consistent association between psychological stress and acne severity highlights the potential value of integrated dermatological and psychological treatment approaches. Stress management interventions, alongside conventional dermatological therapies, may represent an adjunctive strategy for reducing disease severity in susceptible individuals.

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