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Regulatory Mechanism of the HPA Axis in Neurogenic Rosacea

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Abstract: ***Neurogenic rosacea is a special rosacea subtype marked by flushing, erythema, telangiectasia and burning pain. Its pathogenesis relies on complicated neuro-immune-skin-barrier crosstalk that remains incompletely understood. As a core neuroendocrine system, the hypothalamic-pituitary-adrenal (HPA) axis participates in disease progression via stress response, neuroinflammation and skin barrier regulation. This review summarizes HPA axis physiology and its crosstalk with nerves, immunity and skin barrier. We highlight key dysregulated pathways in neurogenic rosacea including stress-triggered axis hyperactivation, neurogenic inflammation, skin barrier damage and immune imbalance. Therapeutic strategies targeting the HPA axis and existing research limitations are also discussed, providing evidence for mechanistic study and clinical translation.***

Keywords: Neurogenic rosacea, HPA axis, Hypothalamic-pituitary-adrenal axis, Regulatory mechanism, Neuroinflammation, Skin barrier.

1. Introduction

1.1 Definition and Mechanisms of Neurogenic Rosacea

Rosacea is a chronic inflammatory dermatosis predominantly affecting the centrofacial region, with a global incidence of 1%-5%. As a vital subtype, neurogenic rosacea accounts for approximately 30%-40% of all rosacea cases [1]. Predominantly observed in young-to-middle-aged women, neurogenic rosacea presents a protracted and recurrent disease course. It not only impairs cutaneous appearance, but also predisposes patients to psychological comorbidities such as anxiety and depression, substantially deteriorating patients' quality of life [2].

Accumulating evidence indicates that neurogenic rosacea does not stem from a single etiological factor, but results from dysregulated crosstalk among the nervous system, immune system and skin barrier. At the neural level, up-regulated expression of transient receptor potential channel proteins including TRPV1 and TRPA1 contributes to heightened neuronal sensitivity, which further facilitates the release of neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) [3]. At the immunological level, activation of macrophages and mast cells as well as dysregulated secretion of pro-inflammatory cytokines including IL-1β, IL-6 and TNF-α trigger local inflammatory responses [4]. At the skin barrier level, dysfunction of keratinocytes and down-regulated expression of tight-junction proteins compromise skin barrier integrity, which further fuels the vicious cycle of neuronal hypersensitivity and inflammation [5]. Nevertheless, existing studies mostly focus on direct interactions among local neuro-immune-skin barrier components. Upstream systemic neuroendocrine regulatory mechanisms, especially the hypothalamic-pituitary-adrenal axis, remain under-investigated, leaving the overall pathological regulatory network of this disease incompletely clarified.

1.2 Associative Studies Between the HPA Axis and Cutaneous Diseases

The hypothalamic-pituitary-adrenal (HPA) axis is the primary neuroendocrine system that mediates organismal responses to internal and external stressors. It forms a hierarchical regulatory cascade consisting of the hypothalamus, pituitary gland, and adrenal gland. The hypothalamus secretes corticotropin-releasing hormone (CRH), which induces pituitary adrenocorticotropic hormone (ACTH) secretion and subsequently stimulates the adrenal cortex to synthesize and release glucocorticoids. Meanwhile, glucocorticoids inhibit hormonal secretion from the hypothalamus and pituitary via negative-feedback mechanisms to maintain systemic homeostasis [6]. Beyond stress response, the HPA axis modulates the functions of the nervous, immune and metabolic systems. It establishes tight regulatory connections with the skin through the functional "neuro-endocrine-skin axis" [7]. Accumulated studies have verified that HPA axis dysfunction plays a pivotal role in inflammatory and neurogenic dermatoses such as psoriasis, atopic dermatitis and neurodermatitis. Patients with atopic dermatitis exhibit abnormal cortisol secretion rhythms, leading to impaired skin barrier repair and aggravated inflammation [8]. Up-regulated CRH receptor expression is detected in psoriatic lesions, which drives disease progression by activating local inflammatory cascades [9]. These findings suggest that the HPA axis may participate in the regulation of neurogenic rosacea via analogous mechanisms.

2. Structure and Physiological Regulatory Mechanisms of the HPA Axis

2.1 Core Components and Signal-Transduction Pathways of the HPA Axis

The core regulatory cascade of the HPA axis is characterized by cascade amplification and negative-feedback modulation. Under physiological conditions, paraventricular nucleus neurons in the hypothalamus synthesize and release corticotropin-releasing hormone (CRH). Transported via the hypophyseal portal system to anterior pituitary corticotrophs, CRH activates the cAMP/PKA signaling pathway to promote the synthesis and secretion of adrenocorticotropic hormone (ACTH). ACTH then binds to melanocortin 2 receptor

(MC2R) on the membrane of adrenal cortex zona fasciculata cells, initiating the biosynthetic pathway for cortisol production from cholesterol [10]. As the terminal effector hormone of the HPA axis, cortisol circulates throughout the body, binds to cytoplasmic glucocorticoid receptors (GR), and translocates into the nucleus to modulate target-gene transcription [10,11]. Simultaneously, cortisol suppresses CRH gene transcription in the hypothalamus and ACTH gene transcription in the pituitary through negative-feedback loops, reducing CRH and ACTH release and forming a closed-loop regulatory circuit to sustain hormonal homeostasis [12]. Furthermore, HPA axis function is modulated by central structures including the autonomic nervous system, hippocampus and amygdala. Sympathetic nerve excitation facilitates CRH secretion, whereas parasympathetic activity exerts inhibitory effects [13].

2.2 Interactive Network of the HPA Axis with Nerves and the Skin Barrier

2.2.1 Interplay with the Autonomic Nervous System

Bidirectional tight regulatory crosstalk exists between the HPA axis and the autonomic nervous system (ANS). On one hand, hypothalamic CRH neurons form direct neuronal fiber connections with sympathetic central nuclei. CRH activates preganglionic sympathetic neurons to trigger norepinephrine release and potentiate systemic stress responses [14,15]. On the other hand, norepinephrine released by sympathetic nerves stimulates hypothalamic CRH secretion through β2 receptors, while acetylcholine from parasympathetic nerves inhibits CRH expression via muscarinic receptors, collectively forming a synergistic regulatory network [15]. Such cross-linking enables the HPA axis to integrate neuronal and endocrine signals for coordinated responses to external stressors.

2.2.2 Effects on Skin Barrier Function

The skin serves as a crucial peripheral target organ for the HPA axis. Its physical, chemical and immunological barrier functions are all modulated by glucocorticoids. In terms of physical barriers, glucocorticoids regulate keratinocyte proliferation and differentiation to shape stratum corneum thickness. Physiological concentrations promote keratinocyte apoptosis and stratum corneum turnover, whereas high-dose or long-term exposure suppresses cell proliferation and induces stratum corneum thinning [16]. Meanwhile, glucocorticoids modulate the synthesis of cutaneous lipids (ceramides, cholesterol and fatty acids) to maintain the integrity of stratum corneum lipid barriers [17]. For tight junctions, glucocorticoids govern the transcription and expression of tight-junction proteins via GR, preserving tight junctions among epidermal keratinocytes and epidermal permeability homeostasis [18]. In addition, glucocorticoids restrain local cutaneous release of inflammatory cytokines and neuropeptides, mitigating barrier damage induced by inflammation and sustaining barrier homeostasis.

3. Dysregulated Mechanisms of the HPA Axis in Neurogenic Rosacea

3.1 Stress-Induced Excessive HPA Axis Activation

Symptom flares of neurogenic rosacea are closely associated with psychological and environmental stressors. Excessive activation of the HPA axis, the core stress-responsive system, may act as an important initiating factor for disease onset. Clinical investigations demonstrate that patients with neurogenic rosacea exhibit substantial psychological stress burden, with significantly higher anxiety and depression scores compared with healthy controls. Moreover, the frequency of stressful events correlates positively with disease severity [19]. Endocrine assays reveal markedly elevated serum CRH, ACTH and cortisol concentrations in patients, accompanied by disrupted cortisol secretion rhythms such as disturbed diurnal patterns and delayed post-stress recovery [20]. In-vitro experiments further show that psychological-stress mimicking interventions (cortisol treatment of keratinocytes) induce disease-relevant phenotypic alterations, implying that stress-driven HPA axis hyperactivation may initiate disease progression via hormonal abnormalities [21].

3.2 Key Pathways for HPA-Axis-Mediated Neurogenic Inflammation

3.2.1 Modulation of Neuropeptide Release

Neuropeptides including substance P and CGRP are core mediators of neurogenic inflammation, and the HPA axis directly regulates neuropeptide synthesis and release via glucocorticoids [22]. Elevated concentrations of substance P and CGRP are detected in lesional skin and peripheral blood of neurogenic rosacea patients, which positively correlate with scores of flushing and burning sensations [23]. Mechanistically, high cortisol concentrations relieve GR-mediated transcriptional repression, thereby de-repressing neuropeptide gene transcription in sensory neurons and enhancing neuropeptide synthesis. Meanwhile, cortisol augments the excitability of sensory nerve terminals to facilitate neuropeptide liberation [22]. Released substance P binds to NK1 receptors on mast cells and endothelial cells in the skin, triggering vasodilation, increased vascular permeability and inflammatory cell infiltration.

3.2.2 Synergistic Regulation with TRPV1/TRPA1 Channels

TRPV1 and TRPA1 are pivotal channel proteins mediating cutaneous sensory and inflammatory signaling. Their aberrant expression and activity underlie neuronal hypersensitivity in neurogenic rosacea [23]. In-vitro assays demonstrate that high cortisol concentrations promote TRPV1 and TRPA1 gene transcription in keratinocytes through GR signaling, and potentiate channel protein phosphorylation to lower stimulation thresholds. Conversely, GR antagonists markedly abrogate cortisol-induced up-regulation of these channel proteins [24]. This synergistic modulation reduces cutaneous thresholds for stimuli such as high temperature and spicy food, eliciting abnormal sensations and neuropeptide release, and amplifying the vicious cycle of inflammation and clinical manifestations.

3.3 Skin-Barrier-Disrupting Effects of the HPA Axis

Impaired skin barrier represents a key pathological hallmark of neurogenic rosacea. Cortisol abnormalities secondary to

HPA axis over-activation may serve as a critical driver of barrier disruption. Lesional skin of neurogenic rosacea patients displays significant stratum corneum thinning, reduced skin hydration and elevated transepidermal water loss, indicating compromised physical barrier function [25]. Mechanistically, excessive cortisol disrupts skin barrier integrity through multiple actions: inhibiting keratinocyte proliferation and differentiation to impair stratum corneum turnover and reduce stratum corneum thickness; down-regulating transcription and expression of tight-junction proteins to disrupt inter-keratinocyte tight junctions and increase cutaneous permeability; suppressing cutaneous lipid synthesis and impairing stratum corneum lipid barrier integrity [26]. The compromised skin barrier fails to block external irritants and inflammatory factor infiltration, further activating sensory nerves and immune cells, exacerbating neuronal hypersensitivity and inflammatory responses, and establishing a self-perpetuating vicious cycle: barrier damage aggravates inflammation, which in turn worsens barrier impairment.

3.4 Interplay Between the HPA Axis and Immune-Inflammatory Cytokines

The HPA axis modulates immune-inflammatory cytokine balance via glucocorticoids, and disruption of this balance sustains persistent inflammation in neurogenic rosacea. The HPA axis participates in inflammatory dysregulation by governing mast-cell activation. Lesional skin of neurogenic rosacea patients presents increased mast-cell counts and elevated degranulation rates [27]. High cortisol concentrations induce GR desensitization, abolishing inhibitory constraints on mast-cell degranulation and promoting the release of histamine, tryptase and pro-inflammatory cytokines, which further amplify local inflammation and vasodilation [28].

4. HPA-Axis-Targeted Therapies for Neurogenic Rosacea

4.1 Pharmacological Therapies

4.1.1 Glucocorticoid Modulators

Glucocorticoid modulators exert therapeutic effects by regulating HPA-axis function or glucocorticoid activity, while careful balance between efficacy and safety is mandatory. Systemic glucocorticoids are reserved for patients with severe acute exacerbations. Short-term low-dose administration rapidly suppresses HPA-axis hyperactivation and inflammatory responses. However, long-term use carries risks including skin atrophy, steroid dependence and HPA-axis suppression, and should be avoided [29]. Topical glucocorticoids directly act on lesional skin to restrain local inflammation and neuropeptide release, yet long-term application may likewise aggravate skin barrier damage. Selective glucocorticoid receptor modulators preferentially bind GR to counteract excessive glucocorticoid signaling while preserving physiological GR functions. Preliminary clinical studies report their capacity to ameliorate flushing and burning sensations with fewer adverse events compared with conventional glucocorticoids, though large-sample clinical trials are still required for validation [30].

4.1.2 Neuropeptide Receptor Antagonists

Given neuropeptide pathways modulated by the HPA axis, neuropeptide receptor antagonists constitute an important therapeutic direction. Anti-CGRP antibodies bind CGRP to block its receptor interactions, inhibiting vasodilation and neuronal hypersensitivity. NK1 receptor antagonists targeting substance P suppress substance-P-mediated inflammation and vascular reactions [31].

4.1.3 Skin-Barrier-Repairing Agents

Skin-barrier-repairing agents break the vicious cycle of barrier-damage-driven inflammation. Repair-oriented moisturizers supplemented with ceramides, cholesterol and fatty acids replenish stratum corneum lipids and up-regulate tight-junction-protein expression to alleviate cutaneous erythema. A randomized controlled trial demonstrated that 8-week continuous application of barrier-repairing moisturizers significantly improved skin barrier function and reduced scores for flushing and burning sensations [32]. In addition, formulations containing panthenol (vitamin B5) soothe cutaneous inflammation and mitigate neuronal hypersensitivity as adjuvant therapies [33].

4.1.4 Regulatory Therapy Using Traditional Chinese Medicine

Traditional Chinese medicine modulates the HPA axis via multi-component active substances, which target different HPA-axis components to relieve chronic stress and ameliorate neurogenic inflammation. Multiple TCM monomers and compound preparations effectively reduce plasma ACTH and corticosterone levels and up-regulate GR expression, thus inhibiting excessive HPA-axis activation. For instance, asiaticoside D (ASD) extracted from Polygala tenuifolia markedly lowers plasma corticosterone and ACTH concentrations and mitigates anxiety-like behaviors in Alzheimer's-disease model rats, confirming its modulatory effects on HPA-axis activity. Astragaloside IV (AST), the major active constituent of Astragalus membranaceus, down-regulates mRNA expression of amyloid precursor protein (APP) and β-secretase to reduce β-amyloid (Aβ) generation and alleviate glucocorticoid-elicited hippocampal neuronal injury [34]. Although most of these findings originate from neurological-disease models, the uncovered core mechanisms of TCM-mediated HPA-axis regulation (inhibition of axis-hormone release, enhancement of receptor function and neuronal protection) provide critical references for interpreting how TCM alleviates stress-related symptoms and mitigates neurogenic inflammation in rosacea patients.

5. Summary

As a vital subtype of rosacea, neurogenic rosacea manifests predominantly as paroxysmal centrofacial flushing, burning, stinging and persistent erythema, and its onset is tightly linked to emotional and environmental triggers. This review systematically elaborates intrinsic correlations between neurogenic rosacea and hypothalamic-pituitary-adrenal axis dysfunction. It highlights that the HPA axis exerts core roles in disease initiation and progression by mediating stress responses, regulating neurogenic inflammation, modulating

skin barrier integrity and governing immune homeostasis. Despite diversified emerging therapeutic strategies targeting the HPA axis (including psychological intervention, targeted pharmacotherapy and TCM modulation), the complete regulatory network remains incompletely elucidated and substantial challenges persist for clinical translation. Future research should integrate basic mechanistic findings and clinical evidence to deepen understanding of crosstalk within the neuro-endocrine-skin axis, facilitating precision-based and individualized management for this disease.

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