

NEUROCUTANEOUS TARGETS IN ACNE: MOLECULAR PATHWAYS FOR PRECISION NEUROCOSMETIC THERAPY

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Introduction

Acne vulgaris remains a therapeutic challenge, with poor adherence driven by delayed results, flares, and side effects especially among adolescents. Beyond excess sebum and bacterial overgrowth, recent evidence highlights the role of neural and neuroendocrine signals. Advances in skin neurobiology now reveal that the molecular pathways behind inflammation, barrier dysfunction, and sebum production are more intertwined than ever imagined. Neurogenic inflammation and dysregulated signaling via CRH, substance P, and TRP channels play a central role in acne pathogenesis. Emerging neurocosmetics including cannabinoids, lipopeptides, and other natural compounds can modulate these pathways, rebalance the microbiome, and restore skin homeostasis. These findings reflect a broader shift toward precise, mechanism-based interventions poised to transform not only acne treatment but also the future of dermatologic and age-related therapies.

Purpose

This project aims to map the key neurocutaneous signaling pathways (CRHR1/2, CB2, TRPV1, PAR-2, NKR) involved in acne pathogenesis, and to propose a molecular-based framework for developing precise, target-specific neurocosmetic therapies. Targeting these pathways offers a mechanistic framework for precise topical intervention in acne.

Methods

This work is a conceptual integration of recent experimental, clinical, and translational evidence related to cutaneous neuroendocrine signaling in acne vulgaris. To construct the proposed pathophysiological and therapeutic model:

Literature Selection:

A focused selection of primary research articles and reviews published in peer-reviewed journals from 2010 to 2024 was performed. Sources were identified through PubMed and Web of Science using key terms such as “acne neuroendocrinology,” “cutaneous CRHR1/2,” “PRLR skin,” “cannabinoid receptors sebaceous gland,” “NK1R dermatology,” and “neurocosmetics.” Preference was given to studies elucidating molecular and cellular mechanisms, receptor expression and signaling in human skin and skin models, and translational works linking these pathways to candidate topical interventions.

Data Extraction and Synthesis:

Molecular mechanisms underlying CRHR1/2, PRLR, CB2/TRPV, and NK1R signaling in sebaceous glands, keratinocytes, and immune cells were systematically extracted. Functional, regulatory, and crosstalk relationships were mapped, emphasizing their relevance to acne pathogenesis and potential topical pharmacological targeting. Contradictory findings were noted and the weight of evidence was appraised qualitatively.

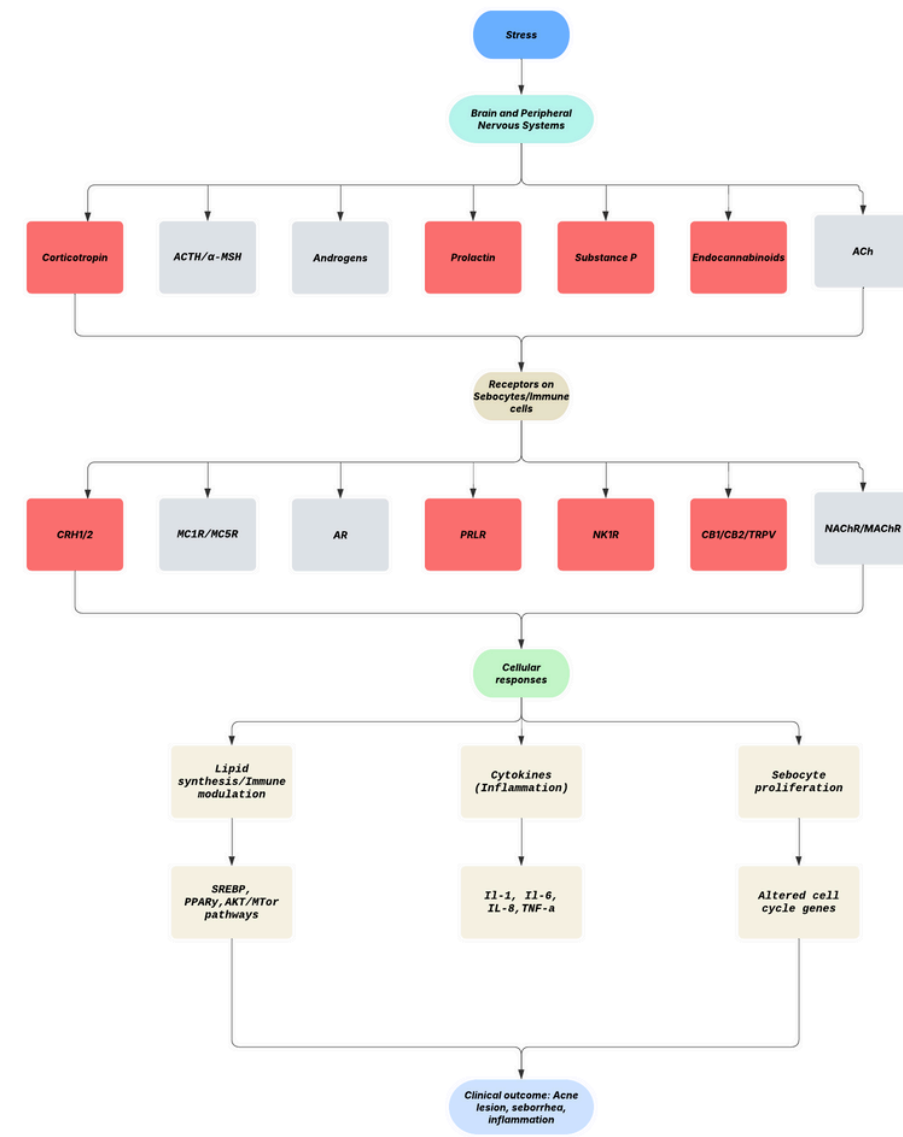
Model Construction:

An integrative diagrammatic model was developed to represent convergent neuroendocrine circuits in the skin relevant to acne. The model identifies actionable receptor targets for emerging neurocosmetic strategies, with each component referenced to its supporting literature.

Justification of Therapeutic Targets:

Candidate receptors were prioritized based on human expression data, functional relevance in recent studies, and emerging pharmacological or topical modulation evidence. Only receptors with sufficient mechanistic and translational support were included in the main model figure.

Mechanisms



*Red boxes indicate novel neuroendocrine targets under current investigation for topical therapeutic modulation in acne.

Results

Receptor/Pathway	Example Drugs/Compounds	Mechanism of Action	Therapeutic Effect	Level of evidence
CRHR1/CRHR2	Antalarmin, α-helical CRH, Arestressin	Antagonists/blockers of corticotropin-releasing hormone receptors—block CRH-induced lipid synthesis and cytokine (IL-6, IL-8) production in sebocytes.	↓ Sebum, ↓ inflammation, improved barrier	In vitro (human sebocyte lines, explants, organ cultures); animal models; p<0.01 vs control for lipid/cytokine reduction; Evidence quality: Strong mechanistic, translational
PRLR	Δ1-9-GI29R-hPRL (PRLR antag.), bromocriptine	Competitive antagonism of PRLR; bromocriptine reduces systemic PRL. Both decrease lipid synthesis and gland proliferation.	↓ Sebum, normalized gland size	Cell/organoid models: p<0.05 reduction in lipids/cell growth; Clinical extrapolation – improved seborrhea with systemic PRL reduction (case series, n=10-30); Moderate evidence
NK1R	Aprepitant, L-733,060, CP-96345	Antagonists of NK1R block Substance P signaling, reducing inflammatory cytokine and lipid production in sebocytes.	↓ Lesions, ↓ inflammation, ↓ sebum	Preclinical (cultured sebocytes, human explants); p<0.05 for cytokine suppression; Clinical: small case series for skin inflammation/itch; Emerging—needs RCTs in acne
CB1/CB2	Rimonabant (CB1 antag.), JWH-133 (CB2 agonist), phytocannabinoids (CBD)	Modulate endocannabinoid signaling—blockade of CB1/CB2 reduces sebocyte lipogenesis; CBD acts principally via TRPV4	↓ Sebum, ↓ cytokines, anti-inflammatory	In vitro (sebocyte lines): CBD p<0.01 for lipid/cytokine reduction; Pilot clinical data CBD cream: significant improvement (Derm/Flu-20, p<0.05); Good translational evidence
TRPV1/2/4	Capsazepine (TRPV1 antag.), CBD (TRPV4 agonist)	Modulate vanilloid signaling, block Ca ²⁺ influx; CBD via TRPV4 reduces lipid synthesis/inflammatory mediators	↓ Sebum, improved barrier, anti-inflammatory	Human sebocyte/explant models: p<0.01 for lipid/inflam reduction; Pilot human trials of topical CBD: clinical improvement, barrier repair (p<0.05); Growing clinical support

Pharmacological modulation of skin neuroendocrine receptors—CRHR1/2, PRLR, NK1R, CB1/CB2, and TRPV—demonstrates significant reductions in sebaceous lipogenesis and inflammatory signaling in preclinical human skin and sebocyte models (typically p<0.01). Pilot clinical data on topical cannabidiol (CBD) and NK1R antagonists indicate promising improvements in lesion count and skin barrier, supporting ongoing development of targeted neurocosmetic interventions.

Conclusion

- Cutaneous neuroendocrine pathways—including CRHR1/2, PRLR, NK1R, CB1/CB2, and TRPV receptors—play central roles in regulating sebum production, inflammation, and skin barrier integrity in acne.
- Pharmacological modulation of these targets has demonstrated significant inhibition of sebum production and inflammatory signaling in preclinical studies, with early clinical data supporting improved skin outcomes.
- Targeting these receptors represents a promising strategy for next-generation, mechanism-based topical therapies and neurocosmetics in acne management.
- A better understanding and translation of these signaling pathways could enable more selective, effective, and well-tolerated treatments for patients with acne vulgaris.

References



Integrating neuroendocrine science into acne therapy opens new avenues for precision, efficacy, and innovation in dermatological practice.