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Brain-Skin Connection: Considerations for Novel Therapies for Skin Diseases

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Abstract

The brain-skin connection has been a topic of growing interest in the neuroscience and dermatology communities. Research has suggested a bi-directional relationship between the brain and skin. They share a common embryologic origin as both are derived from ectoblast differentiation and the skin has a fully functional peripheral equivalent of the Hypothalamic-Pituitary-Adrenal Axis (HPA) which allows it to maintain homeostasis and interact with the brain. Additionally, serotonin (5-HT), which is a well-known neurotransmitter, has been shown to act as a mediator between the skin and the neuroendocrine system. In the skin itself, 5-HT, which can be produced or metabolized by several skin cells, is involved in vasodilation, inflammation, and immunomodulation. The skin serves a neuroendocrine function through its role in maintaining homeostasis and its communication with the central neuroendocrine system. This connection also establishes that psychological stress can have effects on skin including the development or exacerbation of skin diseases such as melanoma and psoriasis. As our knowledge of the brain and neuroendocrine system grows, so does our understanding of this brain-skin connection. Therefore, exploring the role of the brain-skin connection can help establish efficacious long-term therapeutic avenues for the treatment of skin diseases.

1. Introduction

Recent research has focused on the 'brain-skin' axis as a complex interplay between the nervous, endocrine, and immune systems, emphasizing the underlying pathophysiological mechanisms by which psychological stress influences skin homeostasis and clinical applications of this relationship[1]. Perceived psychological stress has become widely known as a force that disrupts the dynamic equilibrium between the nervous, endocrine, and immune systems, thereby triggering and aggravating disease manifestation[2]. It has also been established in the past decade that the skin has a fully functional equivalent to the Hypothalamus-Pituitary-Adrenal Axis (HPA). This finding is crucial because it parallels how other parts of the body utilize the HPA axis to maintain homeostasis. It also shows a potential bidirectional relationship between the neuroendocrine system and the skin. The interplay between this HPA and the other systems can be explained by the schematic in Figure 1, which shows how stress impacts the three axes and what downstream effects result from stress. Suggested routes of the skin-brain axis include the immune system, HPA axis, and the peripheral and central nervous system[3]. The skin can be said to be a "diagnostic window into the brain." The 'brain-skin' connection is complex because of the skin's ability to produce its own serotonin (5-HT) and neurotrophins due to its common embryonic origin with the brain[4].

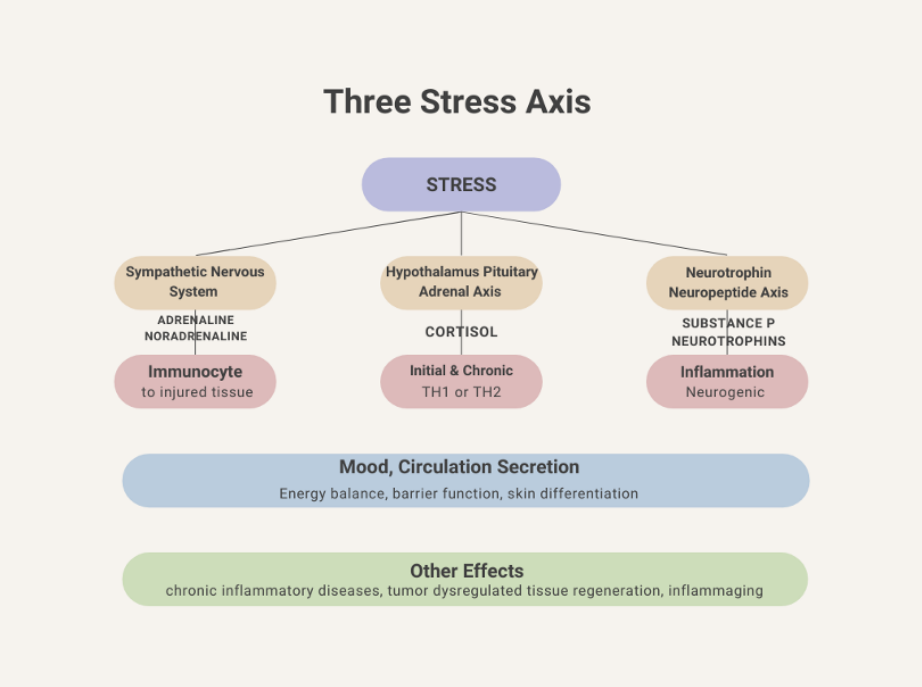

Figure 1: Schematic Representation of the Three-Stress Axis. *This includes the Sympathetic Nervous System, HPA Axis, and Neurotrophin-Neuropeptide Axis.*

Our current knowledge of the 'brain-skin' axis has been derived from technological advances. Graph Theory is used to assess coordinated brain activity and estimate the efficiency of information flow[5]. It has been mathematically applied to psychosocial stress[5]. Salivary cortisol, heart rate, and skin conductance are indices of stress, and psychosocial stress was associated with a decrease in the efficiency of the flow of information within the brain[5]. Functional neuroimaging, especially functional magnetic resonance imaging (fMRI), has enabled indirect visualization of brain function, which has been crucial for understanding more about this bidirectional relationship. A recent study has concluded that sensory testing, skin biopsy, and brain imaging show additional promise as pain biomarkers and should be considered for possible inclusion in the design of clinical trials of pain treatments[6]. Another study utilized fMRI to demonstrate cerebellar activity and connectivity in skin-picking disorder, which is now known to be a potentially maladaptive emotion regulation strategy[7]. Prior to fMRI research, electroencephalography (EEG) was widely utilized, dating back to studies in the 1950s investigating brain activity in syphilis patients. On the other hand, positron emission tomography (PET) allowed scientists to indirectly measure hemodynamic changes. Notably, fMRI has helped

scientists make strides in establishing their knowledge of crosstalk between the skin and the brain's HPA axis.

Many common skin diseases are worsened by stress, and itch (pruritus) is the most well-known symptom associated with inflammatory skin diseases. Several candidate molecules of this stress response, including corticotropin-releasing hormone (CRH) and mast cells, have been shown to have strong pruritogenic potential[1.] Mast cells, white blood cells that are abundant in the skin, occupy a switchboard position and play critical roles in regulating neurogenic inflammation during stress responses[1]. Furthermore, there has been research showcasing close interactions between the nervous and immune systems in the regulation of peripheral inflammation which links stress with chronic somatic disease and aging[8]. Emerging data suggests that chronic inflammations lead to the pro-inflammatory status, known as inflammaging, which underlies premature aging[8,9]. It is important to note that dynamic equilibrium disruptions among these systems can also be referred to as maladaptive plasticity. Maladaptive plasticity induced by neuroendocrine mediators promotes inflammaging and it is believed that neurotrophins, neurotransmitters, and neuropeptides play a potential role in this process[9].

2. Mechanism of the Brain-Skin Connection

The skin is perhaps most well-known for its role as a physical barrier from the environment which requires it to have precise calibration and a high degree of local autonomy to perform daily functions. Highly localized responses are coordinated partly by a skin neuroendocrine system that can reset adaptation mechanisms through either rapid (neural) or slow (humoral) pathways[10]. These pathways can act on local or systemic levels[10]. Cutaneous responses have a primary goal of protecting, restoring, or maintaining homeostasis and dynamic equilibrium with other systems[11]. Its fundamental functions are believed to have originated from its embryonic origin. However, under evolutionary pressure, it has been suggested that autoregulatory circuitry may have undergone specialization and separation resulting in new functions[10]. A variety of different neuromodulators involve in this connection, resulting in many proposed canonical and noncanonical pathways[10].

One way the skin modifies homeostasis is through direct and indirect stimulation of the adrenal cortex (Figure 2). Psychological stress induces many downstream effects. For example, stress results in an increase in glucocorticoids which decreases differentiation and proliferation, thereby decreasing lipid synthesis, lamellar body production in the skin and ultimately resulting in abnormal permeability and abnormal stratum corneum integrity and cohesion. Skin disorders are sometimes adversely affected by psychological stress and are frequently characterized by this defective cutaneous permeability barrier function[10]. This is due to the reduced density of lamellar bodies. The barrier to pathogenic microbes is also impacted because psychological stress reduces epidermal AMP levels, which are needed to decrease the growth of microbes[10]. This ultimately results in increased severity of infections due to abnormalities brought on by psychological stress.

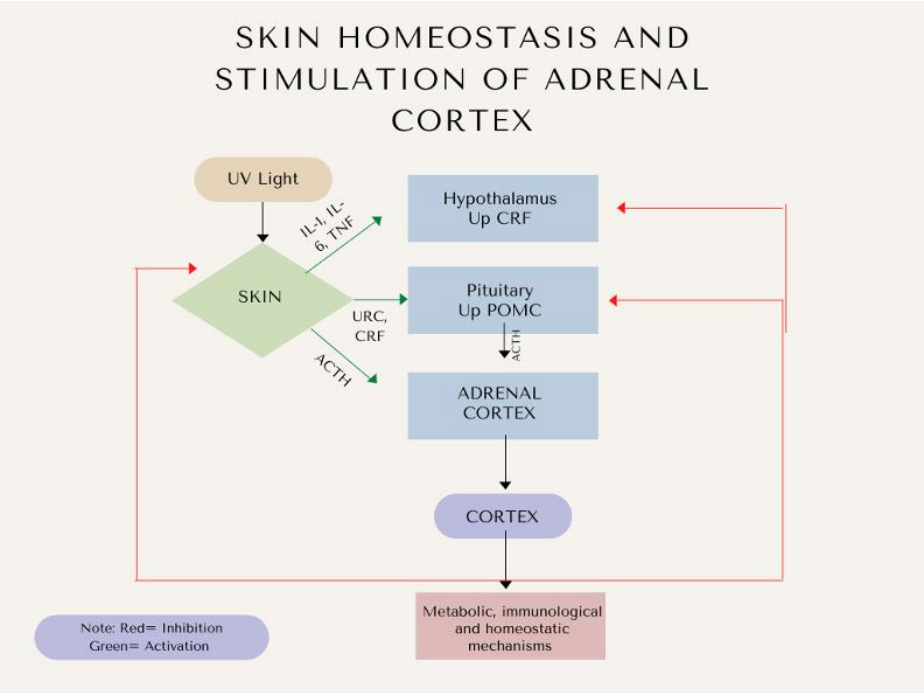

Figure 2: Flowchart Demonstrating How Skin Modifies Body Homeostasis Through Direct and Indirect Stimulation of the Adrenal Cortex. *Red lines indicate inhibition and green lines indicate activation. IL represents interleukins, which aid T cells. TNF is a tumor necrosis factor. URC stands for urotropins and CRF for corticotropin releasing factor. ACTH stands for acetylcholine. POMC is pro-opiomelanocortin, which is a precursor to ACTH.*

Furthermore, there have been observations suggesting corticotropin-releasing factor (CRF) driven responses are another important component

to the mechanism of the brain-skin connection[10]. These are properties displayed most clearly by neural crest-derived melanocytes and hair follicles which have activation sequences that closely reproduce basic features of the central HPA axis[10]. CRF1 and CRF2 are receptors of CRF and may have unique characteristics and effects. This is especially interesting to explore as there are differential expressions of isoforms of CRF1 resulting in coupling to different sets of signal transduction pathways. Many current research projects are investigating the effector functions of CRF1 and CRF2 agonists and antagonists, specifically in their regulation of keratinocytes, cells that produce keratin, and immunocytes, cells that produce antibodies, activities.

Skin biomarkers for organ-specific diseases are another area of current research. It has recently been elucidated that alterations of the Wnt signaling pathway may predict the aging status of the cardiovascular system, the brain, and bones[11]. This signaling pathway is well known in the scientific community for its role in cell determination. Advanced glycosylation end-products (AGE) and Wnt pathway proteins are considered laboratory biomarkers for systemic disorders and are believed to be gender-independent[11]. Other intrinsic and extrinsic parameters may also influence aging, but this process is highly variable on an individual basis[11].

Another important contributor is UV energy. As UV light is absorbed by the skin, many downstream effects occur, resulting in mechanisms that defend skin integrity and induces skin pathology such as cancer. Exposure to UV radiation is the principal cause of nonmelanoma skin cancer, a process in which serotonin (5-HT) is intimately involved[12]. The skin is a target for neuroendocrine signals from circulation and via nerve endings. It is believed that the UV touches the brain and central neuroendocrine system to reset body homeostasis[13]. There are three biologically relevant spectra of UV, including UVC (200-280 nm), UVB (280-320 nm), and UVA (320 to 400 nm). Among these, UVC is profoundly mutagenic and is absorbed by the stratum corneum[13].

UV is believed to stimulate both the intracutaneous and the cutaneous HPA (cHPA) axis through neural and humoral mechanisms which are wavelength dependent and rely on anatomical structures sensing UV energy[14]. Outside of this function, UVA and UVB light also stimulates the opioidergic system,

specifically stimulating β-endorphin levels in the skin and the brain[14]. UV-induced immunosuppression is triggered via a cascade that begins with cis-urocanic acid—an immune modulator produced in the stratum corneum that binds to the 5-HT receptor[14]. These connections provide another mechanism to explore and therapeutically target.

3. Brain-Skin Connection and Melanoma

The brain-skin connection is key in explaining how and why psychological stress can impact the skin[15]. Melanoma is a cancer of melanocytes—cells that give rise to skin tone, hair, and even eye color. It is also one of the most aggressive forms of skin cancer[16,17]. Many individuals with melanoma have brain metastases which are severe complications, and the prognosis for patients with metastasis has a median survival time of 6 months after diagnosis[18]. Melanoma cells can proliferate in the brain parenchyma or the meninges, and in cases where the blood-brain barrier is leaky, the lesions are also resistant to chemotherapeutic drugs[18]. A suggested mechanism involves very late antigen 4 (VLA-4), which regulates immune recruitment to inflamed endothelium. VLA-4 mediated adhesion of melanoma cells on the blood-brain barrier serves as a cue for melanoma cell intercalation and disruption of the barrier[16]. 92% of all human melanoma brain metastases stained VLA-4 positive[16]. This finding has further implications for multiple sclerosis as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), expressed at high levels during inflammation when VLA-4 is expressed, contribute to the development of autoimmune encephalomyelitis (EAE)[16].

Recently, a reciprocal relationship has been demonstrated between Parkinson's Disease (PD) and melanoma[19]. This is a relationship wherein PD patients are more susceptible to melanoma and vice versa. The current framework and hypothesis suggest that α- synuclein modulates the aggregation of Pmel17, a functional amyloid that serves as a scaffold for melanin biosynthesis [19]. Research on α- synuclein can help the scientific community develop novel approaches to treating melanoma but also can reveal insights into its role in PD[19].

4. Psoriasis Pathogenesis and Antipsoriatic Drug Development

Psoriasis is a non-communicable chronic immune-mediated skin disease with pathogenesis derived from both genetic and environmental factors[15]. It has been previously established that 5-HT is a stress mediator that contributes to the effects of psychological stress on the disruption of skin homeostasis in a variety of skin diseases, including psoriasis[15]. Psoriasis is mediated by T lymphocytes with Th1 and Th17 profiles[20]. Some of the main triggers of psoriasis include trauma, non-steroidal anti-inflammatories, infections, and of course, psychological stress[15]. To garner a better understanding of psoriasis, we should first begin by investigating the processes that underlie skin immunity and neuroendocrinology[15]. Psychological stress has been proposed to dysregulate the HPA axis, which thereby exacerbates psoriasis[20]. This is likely due to the release of proinflammatory cytokines and over-activation of the HPA axis[20].

Sunlight deficiency strongly impacts the severity of psoriasis. NB-UVB, narrow-band UVB, is the only currently accepted form of treatment for psoriasis[20]. Vitamin D deficiency is an important factor in the development and progression of psoriasis, and high doses of vitamin D were found to be efficient in eradicating psoriatic plaques[20]. This is also a deficiency that is common in both psoriasis and depression, and there may even be a causal relationship whereby vitamin D deficiency may increase the risk of depression[20].

Mouse models provide the scientific community with a basis for studying psoriasis pathogenesis and antipsoriatic drug development[20,21]. It is not uncommon to utilize animal models to promote the discovery and development of drugs. The mouse model of psoriasis can be divided into spontaneous, genetically engineered (transgenic and knockout), xenotransplantation, and directly induced approaches[21]. Animal models and other research has helped scientists delineate that IL-23 mediates the Th17 cells, which is a key part of the pathogenesis of psoriasis[21].

5. Conclusion

Overall, the scientific community has made significant strides, especially in the past decade, regarding our current knowledge on the 'brain-skin' axis. Psychosocial stress, brought about by multiple factors, is a force that disturbs the dynamic equilibrium established between the nervous, endocrine, and immune systems, thereby triggering and aggravating disease manifestation[1]. There are many complexities intrinsic to these connections. Currently, our understanding includes the sympathetic nervous system, HPA axis, and neutrophin-neuropeptide axis[22]. Animal models and advancements in fMRI technology have contributed to a growing body of knowledge and literature on these mechanisms and their relationships to potential therapeutic applications.

This relationship has demonstrated impacts in research on melanoma and psoriasis as well as other diseases and conditions such as stroke and brain trauma[23]. Future therapeutic avenues include the development of drugs that restore homeostasis in terms of the brain-skin connection, such as current research into agonists and antagonists directed toward 5-HT receptors[24].

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