

Review of the Relationship between Mental Stress and Inflammatory Skin Diseases

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ABSTRACT

Inflammatory skin diseases have a major impact on the psychological state and quality of life of patients, and can lead to an increased burden on the patient's mental state and cause psychological problems such as anxiety and depression. In addition, psychological stress can aggravate the condition of inflammatory skin diseases. Nowadays, the relationship between psychological stress and inflammatory skin diseases has received much attention. Therefore, a review of the relationship between the two is necessary. In this review, we discuss the close relationship between the neurobiological mechanisms of psychological stress and the secretion of proinflammatory cytokines induced by brain-gut-skin communication. We also discuss the mechanisms by which psychological stress may exacerbate inflammatory skin diseases through descending pathways (central and peripheral hypothalamic-pituitary-adrenal axes, peripheral nerves, and skin barrier function).

KEYWORDS

Mental Stress; Inflammatory Skin Diseases; HPA Axes; DMN.

1. INTRODUCTION

Inflammatory skin diseases are difficult to treat and have a long duration, resulting in localised lesions that are visible to the naked eye and cause recurrent itching or pain[1]. These characteristics can lead to a negative attitude to life, social isolation and discrimination. These psychological stressors can affect the patient's attitude to life, work, social interactions and other daily activities[2]. In conclusion, the quality of life of patients with inflammatory skin diseases is significantly affected and, over time, affects the psychological state of the patient[3]. Patients with hidradenitis suppurativa, acne and psoriasis have been found to have a significantly higher risk of anxiety, depression and suicide. In addition, psychological stress can further exacerbate dermatological conditions; psychological stress and continued exacerbation form a vicious circle that can lead to difficulties in managing dermatological conditions, significant impairment of quality of life and the development of psychological problems[1,4]. It is therefore imperative that the neurobiological mechanisms are clearly articulated and that the primary problem is identified and addressed with effective interventions. Over the past 20 years, research in neurobiology has advanced dramatically. Neuroimaging research has also been very helpful in clarifying the structural basis of negative depression[4,5]. Researchers have also found that the overexpression of pro-inflammatory cytokines in the bloodstream has a clear positive correlation with the development of negative, depressive and anxious mood. Animal and human studies also provide strong evidence that stressful conditions can worsen skin diseases. Recently, the link between mental stress and inflammatory skin diseases has received a lot of attention, so it is necessary to review the relationship between the two. In this article

we present a brief review of the neurobiological relationship between mental states and inflammatory skin diseases.

2. PRO-INFLAMMATORY CYTOKINES AND MENTAL HEALTH

Numerous studies have shown that pro-inflammatory cytokines (e.g. IL-1, IL-6 and TNF- α) are significantly elevated in the blood of depressed patients[6]. These cytokines can also induce depressive thoughts or depressive states in healthy people[2,7]. In studies in which the endotoxin *Salmonella abortus equi* or a control was administered intravenously to healthy subjects 1-2 hours later, IL-6, TNF- α and scores on questionnaires assessing symptoms of anxiety and depression were found to be significantly elevated. Animal studies have shown that administration of lipopolysaccharide (LPS) induces depressive-like behaviour and elevated levels of IL-6[5,8]. In addition, there was a significant improvement in depressive symptoms following a reduction in pro-inflammatory cytokine levels. The occurrence of negative thoughts during difficult problems was significantly increased in healthy people with high levels of IL-6[1,2,9]. These results suggest that high levels of pro-inflammatory cytokines may lead to negative thoughts and depression[1,7,10]. Meanwhile, patients with inflammatory skin diseases had significantly higher levels of pro-inflammatory cytokines. TNF- α was also found to be significantly elevated in lichen planus, acne vulgaris and psoriasis. The TNF- α antagonist etanercept has been shown to significantly improve depressive symptoms in patients[1,4,11]. This improved psychological state may also correlate with improved psoriasis and systemic inhibition of TNF- α [1,5,8,12]. In mice without skin disease, etanercept treatment significantly improved anxious and depressive behaviour[2,7,10,13]. Therefore, the relationship between inflammatory cytokines and mental health status in patients with inflammatory skin diseases needs to be confirmed by further studies.

3. PRO-INFLAMMATORY CYTOKINES IN THE BLOOD

Intestinal epithelial cells form the intestinal barrier, which connects to other tissues through a complex network of proteins and prevents harmful substances in the gut from being absorbed by the body into the bloodstream[2,6,14]. In addition, normal gut flora can help protect against invading pathogenic microorganisms by stimulating the secretion of mucus, zonulin and occludin from the intestinal tract[2,3,6,15]. Psychological stress can lead to over-absorption of harmful substances by disrupting the intestinal barrier (i.e. leaky gut)[2,4,8,16]. Psychological stress has been shown to increase the uptake of fluorescein isothiocyanate dextran (FITC-dextran) into the bloodstream[2,4,9,17]. One possible mechanism is that stress causes leaky gut by disrupting the intestinal flora. Physiologically, intestinal mucus secretion is an effective barrier to microorganisms in the intestinal epithelium and intestinal tract. In contrast, stress induces a decrease in mucus secretion, allowing microbes to come into direct contact with intestinal epithelial cells and the intestinal barrier, which further leads to the entry of intraluminal entities (e.g. bacteria, pathogens, viruses and toxins) into the bloodstream, inducing a cascade of inflammatory responses and the production of pro-inflammatory cytokines[1,3,18]. In leaky gut, bacterial endotoxins such as LPS can also cross the intestinal barrier and stimulate the secretion of pro-inflammatory cytokines by intestinal fibroblasts, and a vicious cycle of bacterial entry into the circulation can occur through the break down of the intestinal barrier[19,20]. Patients with inflammatory skin diseases may produce pro-inflammatory cytokines via the gut-brain axis due to psychological stress. The leaky gut phenomenon has been confirmed in patients with chronic inflammatory skin diseases such as AD, PN and psoriasis. In AD patients, improving the intestinal barrier by supplementation with probiotics may also improve the AD condition[2,21].

When the internal environment of the gut is altered by the above disturbances, the gut can send signals to the brain via vagal afferent fibres[11,22]. The brain perceives the signals and then regulates the gut

environment through various signalling pathways, including efferent vagal nerve fibres. However, these mechanisms are significantly diminished in patients with depression and IBD[3,23]. Promoting the restoration of vagal function and tone by stimulating the vagus nerve can effectively reduce levels of pro-inflammatory cytokines and improve depression[7,8,24]. In depressed patients, reduced vagal tone is also a possible cause of elevated levels of pro-inflammatory cytokines. However, whether reduced vagal function occurs in patients with inflammatory skin diseases needs to be further investigated[2,6,25]. Dysfunction of the central hypothalamic-pituitary-adrenal (HPA) axis may also explain the significantly elevated levels of pro-inflammatory cytokines in patients with depression or inflammatory skin diseases. Pro-inflammatory cytokines are significantly elevated in the blood under stressful conditions[3,5,26]. Cortisol can effectively inhibit these cytokines via the HPA axis. Cortisol secretion is insufficient in stress patients compared to healthy individuals, resulting in high levels of pro-inflammatory cytokines in the blood. It has also been found that HPA function is also deficient in inflammatory skin diseases such as AD (i.e. blunted cortisol associated with psychological stress)[1].

4. PERIPHERAL PRO-INFLAMMATORY CYTOKINES AND THE BRAIN

The brain consists of a variety of cells and receives oxygen and nutrients from the blood through blood vessels[7,13]. In particular, the blood vessels of the brain can regulate the entry of certain substances into the brain tissue by the construction of the blood-brain barrier (BBB), which protects the brain tissue from the entry of harmful substances or macromolecules[10,18]. However, the mechanism by which inflammatory cytokines, which are peptides, enter the BBB is not clear. In one study, radiolabelled IL-6 (or TNF- α) was injected into the peripheral blood vessels of animals and it was found that IL-6 (or TNF- α) could enter the brain across the BBB[8,19]. Psychological stress can inhibit the tight junctions of cerebral vascular endothelial cells and thus inhibit BBB function[2,19]. Therefore, patients with inflammatory skin disease may have more pro-inflammatory cytokines entering brain tissue due to altered mental status[7,13]. The upregulated levels of pro-inflammatory cytokines in the blood may also further promote cytokine release by acting on the vascular endothelial cells of the BBB[8]. The entry of cytokines into brain tissue could further promote microglia and amplify the inflammatory response[7]. By activating cytokines, the release of cytokines within the brain is widely considered to be neuroinflammation. Microglia can act directly on dendritic spines or axonal terminals of neurons to modulate plasticity in brain circuits, thereby affecting environmental homeostasis (e.g., homeostasis) as well as adaptive environments (e.g., learning)[2,5,6]. It is currently thought that neuroinflammation induces changes in neuroplasticity that affect psychological states.

5. THE DEFAULT MODE NETWORK (DMN) AND NEGATIVE THOUGHTS

In daily life, humans often recall recent and future emotional events and think to themselves in order to assess them[3]. People use 50% of their waking hours each day to meditate[5]. Previous studies have shown that although people meditate frequently, most of the time their thoughts are mainly negative or they fall into contemplation[6,7]. If this happens on a regular and consistent basis, it can lead to a negative mental state[2]. For each individual, the intensity of the expression of negative symptoms is closely related to mind-wandering[3]. Some studies have found higher levels of mind-wandering in depressed patients with clinical or subclinical manifestations[3,5]. Recently, researchers have identified an intracerebral network, the DMN (consisting of the medial parietal cortex, inferior parietal cortex, temporal cortex and medial prefrontal cortex), that is closely associated with mind-wandering[1,3,7]. The above structures are closely related to memory, self-awareness and directing internal attention[10]. Signaling between the cortexes often occurs to produce mind-wandering[14]. It is now believed that people who often have higher levels of DMN neural activity have more severe negative thoughts about themselves and their lives[5,6]. Studies of patients with chronic pain have found that those with higher levels of DMN activity have more severe and more pronounced negative

memories of pain. Inflammatory skin diseases patients with high DMN activity were found to have a high level of subjective severity of their chronic itch by fMRI studies[1,2]. Inflammatory skin diseases patients with high DMN activity were more likely to have negative thoughts about their disease.

6. OTHER ELEMENTS AND MENTAL STATES

There are other proinflammatory cytokines that are also significantly elevated in the peripheral circulation of inflammatory skin diseases[9,11]. For example, IL-17 is secreted by Th-17 immune cells and is strongly implicated in the pathogenesis of psoriasis and hidradenitis suppurativa[2]. Proinflammatory cytokines such as IL-6 and TNF- α can induce Th-17 cell differentiation and secretion of IL-17 to form a cascade amplification pathway[12]. IL-17 receptors are expressed on several cell types, including vascular endothelial cells of the BBB[2]. In the circulation, IL-17 can bind to vascular endothelial cells of the BBB and induce structural remodelling[3]. This structural remodelling can lead to the migration of various immune cells from the circulation into brain tissue[4]. Recent studies have found that Th-17 and IL-17 may be involved in the pathogenesis of major depressive disorder (MDD) and anxiety, but further work is needed[1,8]. Blood levels of IL-17 have also been found to be significantly higher in depressed patients than in controls[7,9]. One study found that IL-17 levels were significantly higher in rheumatoid arthritis patients than in controls when combined with anxiety, which also suggests to us that IL-17 may be involved in mediating the development of mood disorders[10]. The study of serum IL-17 and IL-23 levels in patients with MDD showed no difference in baseline IL-17 levels[9,10]. And there was no significant change in IL-17 levels after 6 weeks of anti-MDD treatment[11]. Anti-IL-17 treatment can effectively inhibit the release of pro-inflammatory cytokines, and psoriasis patients treated with secukinumab also showed improvement in anxiety and depressive symptoms[1,5].

IL-23 is involved in mediating the production and secretion of a variety of inflammatory factors and can promote the differentiation of Th-17 cells to secrete IL-17 to produce neuroinflammation[6]. Whether IL-23 is involved in the association between mood disorders and skin inflammation remains to be determined[10]. A positive correlation has been found between IL-23 levels and symptoms of anxiety and depression in patients with arthropathic psoriasis[2,4]. In gene expression analysis studies, IL-23 and IL-17 gene expression levels were significantly higher in anxious patients compared to controls.

Adipokines released from white adipose tissue and peripheral vascular endothelial cells also play a role in the pathogenesis of inflammatory skin diseases such as psoriasis and AD[1]. Among the adipokines, resistin, chemerin and leptin have pro-inflammatory effects, whereas adiponectin has anti-inflammatory effects[1,3]. Adiponectin levels are significantly lower in patients with psoriasis and increase after effective treatment. Psoriasis-associated proinflammatory cytokines (e.g. TNF α , IL-1 and IL-6) circulate through the peripheral blood into the subcutaneous adipose tissue to promote chemerin and resistin production[5]. Studies have shown that psoriasis patients have significantly higher levels of pro-inflammatory adipokines, whose receptors are widely expressed in the brain. Leptin and adiponectin can regulate cell proliferation, survival and synaptic plasticity in the hippocampus via the BBB[8]. Adiponectin has also been shown to have modulatory and antidepressant effects on anxiety. Thus, an imbalance in adipokine secretion may be involved in mediating mood disorders and inflammatory skin, but further experiments on inflammation are needed.

7. MECHANISMS OF STRESS-INDUCED AGGRAVATION OF INFLAMMATORY SKIN DISEASES

The brain and skin can communicate through a number of pathways. One of the most important is the hypothalamic-pituitary-adrenal (HPA) axis[1,3]. The HPA is an important pathway that mediates downstream stress responses and is closely involved in the regulation of many physiological functions[4,5]. Under stress conditions, the hypothalamus secretes corticotropin-releasing hormone (CRH) and stimulates the secretion of proopiomelanocortin and adrenocorticotrophic hormone (ACTH) by the hypothalamus, and ultimately cortisol by the adrenal gland[2,5,10]. These hormones play an important role in the body's regulation of the immune response and the skin barrier under stressful conditions[3]. Skin tissue cells (e.g. keratinocytes, mast cells and sebum-producing cells) also have functions similar to those of the HPA, producing CRH, ACTH, cortisol and other hormones with similar functions, mainly in response to mechanical and chemical stimuli[5,6]. These hormones, such as CRH, bind to CRH receptors in the skin and regulate inflammatory pathways. In patients with AD, CRH promotes the differentiation and proliferation of Th2 cells and is involved in mediating inflammation. In patients with psoriasis, antibody binding to CRH receptors on the surface of mast cells can induce degranulation and further increase inflammation by promoting IL-6 and TNF- α secretion[2,7]. Psychological stress may also be involved in exacerbating skin inflammation through the HPA pathway[4,8]. In addition, animal studies have shown that psychological stress may also affect skin barrier recovery and antimicrobial peptide synthesis[9,22]. The brain may also act by affecting local peripheral nerves in the skin[2,24]. Psychological stress can induce remodelling of local peripheral nerve fibre endings in the skin or produce SP effects on immune cells with pro-inflammatory effects (e.g. neurogenic inflammation including mast cell degranulation, CD4 T cell proliferation and IFN-gamma and TNF-alpha production)[2,25]. In a mouse model of stress, local SP+ nerve fibre expression is increased in the skin and can act on mast cells to produce degranulation effects[6,26]. The above mechanisms may be involved in mediating local inflammation and exacerbation of AD skin. Similarly, SP+ nerve fibre expression was found to be significantly higher in the skin of patients with psoriasis compared to the healthy group[11,17,23,26]. In addition, neuropeptide Y (NPY) may also be involved in mediating the development of acute psychological stress and inflammatory skin diseases, but further experiments are needed to clarify the exact mechanism[5].

Psychological stress can further exacerbate scratching behaviour in inflammatory skin disease[9]. Scratching is considered to be one of many substitutive behaviours that can be induced by stress and help to reduce sympathetic excitability to restore homeostasis[7,9]. Stress-induced scratching is more pronounced in patients with chronic inflammatory skin diseases with chronic pruritus[1,3]. The frequency intensity of stress-induced itch scratching was significantly greater in AD patients than in controls. Gastrointestinal dysfunction is also involved in mediating the exacerbation of inflammatory skin diseases[10,11]. Psychological stress can induce a leaky gut and thus promote a circulatory inflammatory response[4]. The leaky gut associated with chronic gastrointestinal disease often leads to inflammatory skin disease and itchy flare-ups, and the skin inflammatory response and barrier are repaired after improvement in gastrointestinal function[4]. The above findings suggest a close link between the brain, gut and skin, which together play an important role in the exacerbation of stress-induced inflammatory skin diseases.

8. CONCLUSION

There is a clear negative correlation between inflammatory skin diseases and psychological stress. However, the exact mechanism is not clear. Inflammatory factors in the peripheral blood circulation and the DMN play an important role in the exacerbation and maintenance of psychological stress induced by inflammatory skin diseases, and the gut-brain-skin axis may serve as a possible link

between these phenomena. The gut-brain-skin axis may serve as a possible correlate of the above phenomena. Inflammatory skin diseases may be mediated by the central and peripheral HPA axes, neurogenic inflammation and stress-induced scratching behaviour exacerbate the psychological stress response and further exacerbate the manifestations of the disease. However, further experiments are needed to verify the relationship between inflammatory skin diseases, psychological stress and the resulting impairment of quality of life and mental health.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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